

## EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	8049	(antithrombin) or (anti-thrombin)	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/11/06 09:05
L2	467	l1 and p3	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/11/06 08:21
L3	16	l1.ab. and p3	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/11/06 08:21
L4	4733	(antithrombin III) or (anti-thrombin III)	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/11/06 09:05
L5	8	l4.ab. and p3	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/11/06 09:05

10516662

File 5:Biosis Previews(R) 1926-2007/Oct W4  
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Set	Items	Description
Set	Items	Description
S1	8872	(ANTI()THROMBIN()III) OR (ANTITHROMBIN()III) OR ATIII
S2	291	(RESISTANCE) AND S1
S3	0	S2 AND P3
S4	0	S2 AND CATHEPSIN
S5	1	S2 AND ELASTASE
S6	0	S2 AND ARG393
S7	18	ARG393
S8	7	S1 AND P3
S9	118526	1 AND MUTAT?
S10	433	S1 AND MUTAT?
S11	94	S2 AND MUTAT?

? t s5/7/1

5/7/1  
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09183216 BIOSIS NO.: 198886023137  
OXIDATIVE INACTIVATION OF PURIFIED HUMAN ALPHA-2 ANTIPLASMIN  
%%ANTITHROMBIN%% %%III%% AND C1-INHIBITOR  
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JOURNAL: Thrombosis Research 49 (6): p581-590 1988  
ISSN: 0049-3848  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: ENGLISH

ABSTRACT: Oxidative inactivation of alpha-1-proteinase inhibitor (A1-PI) and plasminogen activator inhibitor-1 (PAI-1), both members of the serine protease inhibitors superfamily, using mild oxidation and conditions has been already demonstrated. The oxidation mechanism has been shown to involve conversion of methionine to methionine sulfoxide in the reactive center of the inhibitors. In this study evidence is presented that alpha-2-antiplasmin (A2-PI) and %%antithrombin%% %%III%% (AT III) can also be inactivated by means of oxidation. For total inactivation of 50 pM A1-PI about 10 nM chloramine T (CT) and for the same molar concentration of A2-PI and AT III about 250 nM CT were necessary. C1-inhibitor (C1-INH) showed some %%resistance%% to oxidation that could be overcome only by increasing CT to an amount (> 2000 nM) already beginning to inactivate the corresponding C1-esterase. As target enzymes for A2-PI, AT III, and A1-PI plasmin, thrombin and %%elastase%%, respectively, were used. Their activity was not impaired by the oxidation conditions applied. As there is no methionine in the reactive center of AT III an additional mechanism for oxidative inactivation of serpins has to be taken into consideration. Oxidation seems to be a general mechanism for altering the balances between serine proteases and their inhibitors

in favour of the protease.  
? ds

Set	Items	Description
S1	8872	(ANTI( ) THROMBIN( ) III) OR (ANTITHROMBIN( ) III) OR ATIII
S2	291	(RESISTANCE) AND S1
S3	0	S2 AND P3
S4	0	S2 AND CATHEPSIN
S5	1	S2 AND ELASTASE

? s s2 and Arg393

291 S2

18 ARG393

S6 0 S2 AND ARG393

? s Arg393

S7 18 ARG393

? t s7/7/1-5

7/7/1

DIALOG(R) File 5: Biosis Previews(R)

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17746060 BIOSIS NO.: 200400116817

Two novel conserved motifs in the hepatitis C virus NS3 protein critical for helicase action.

AUTHOR: Frick David N (Reprint); Lain Angela M I (Reprint); Keeney David (Reprint)

AUTHOR ADDRESS: New York Medical College, Valhalla, NY, USA\*\*USA

JOURNAL: Hepatology 38 (4 Suppl. 1): p349A October 2003 2003

MEDIUM: print

CONFERENCE/MEETING: 54th Annual Meeting of the American Association for the Study of Liver Diseases Boston, MA, USA October 24-28, 2003; 20031024

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ISSN: 0270-9139 (ISSN print)

DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Superfamily 2 (SF2) helicases and helicase-like proteins share 6 conserved motifs. Alignments reveal that several additional conserved motifs are present in the SF2 helicase encoded by the hepatitis C virus (HCV). The roles of two such motifs are examined here using structure-based site-directed mutagenesis. The first motif (YRGXDV) forms a loop that connects SF2 helicase motifs 4 and 5, at the tip of which is %Arg393%. When %Arg393% is changed to Ala, the resulting protein retains a nucleic acid stimulated ATPase but cannot unwind RNA, unwinds DNA poorly, and does not translocate on ssDNA. DNA and RNA stimulate ATP hydrolysis catalyzed by R393A like the wild-type but the mutant protein binds DNA more weakly than wild-type both in the presence and absence of a non-hydrolysable nucleotide analogue. Thus, this "Arg-clamp" motif anchors the protein on nucleic acid enabling processive unwinding. The second motif (DFSLDPTF) forms a beta-loop between SF2 motifs 5 and 6 that connects domains 2 and 3. When F444 in this "beta-arm" is changed to Ala, the resulting protein is devoid of all activities. When F438 is changed to Ala, the protein retains nucleic acid stimulated ATPase, but unwinds DNA and RNA poorly. In this case, uncoupling of ATP hydrolysis and unwinding is due to the fact that the F438A mutant does not release DNA upon ATP binding like the wild-type. The F438A mutant also has a lower

melting temperature than the wild-type indicating the hydrophobic pocket formed by the beta-arm and residues in domain 3 stabilizes the protein. Data support an inchworm model for helicase action and identify two new potential sites for rational HCV drug design.

7/7/2

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17639308 BIOSIS NO.: 200400020065

Two novel conserved motifs in the hepatitis C virus NS3 protein critical for helicase action.

AUTHOR: Lam Angela M I; Keeney David; Frick David N (Reprint)

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JOURNAL: Journal of Biological Chemistry 278 (45): p44514-44524 November 7, 2003 2003

MEDIUM: print

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The hepatitis C virus (HCV) NS3 helicase shares several conserved motifs with other superfamily 2 (SF2) helicases. Besides these sequences, several additional helicase motifs are conserved among the various HCV genotypes and quasispecies. The roles of two such motifs are examined here. The first motif (YRGXDV) forms a loop that connects SF2 helicase motifs 4 and 5, at the tip of which is %%Arg393%%. When %%Arg393%% is changed to Ala, the resulting protein (R393A) retains a nucleic acid stimulated ATPase but cannot unwind RNA. R393A also unwinds DNA more slowly than wild type and translocates poorly on single-stranded DNA (ssDNA). DNA and RNA stimulate ATP hydrolysis catalyzed by R393A like the wild type, but the mutant protein binds ssDNA more weakly both in the presence and absence of the non-hydrolyzable ATP analog ADP(BeF3). The second motif (DFSLDPTF) forms a loop that connects two anti-parallel sheets between SF2 motifs 5 and 6. When Phe444 in this Phe-loop is changed to Ala, the resulting protein (F444A) is devoid of all activities. When Phe438 is changed to Ala, the protein (F438A) retains nucleic acid-stimulated ATPase, but does not unwind RNA. F438A unwinds DNA and translocates on ssDNA at about half the rate of the wild type. Equilibrium binding data reveal that this uncoupling of ATP hydrolysis and unwinding is due to the fact that the F438A mutant does not release ssDNA upon ATP binding like the wild type. A model is presented explaining the roles of the Arg-clamp and the Phe-loop in the unwinding reaction.

7/7/3

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17513727 BIOSIS NO.: 200300482446

Functional analysis of an inosine-guanosine transporter from Leishmania donovani. The role of conserved residues, aspartate 389 and arginine 393.

AUTHOR: Arastu-Kapur Shirin; Ford Ethan; Ullman Buddy; Carter Nicola S  
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JOURNAL: Journal of Biological Chemistry 278 (35): p33327-33333 August 29,  
2003 2003  
MEDIUM: print  
ISSN: 0021-9258  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Equilibrative nucleoside transporters encompass two conserved, charged residues that occur within predicted transmembrane domain 8. To assess the role of these "signature" residues in transporter function, the Asp389 and Arg393 residues within the LdNT2 nucleoside transporter from Leishmania donovani were mutated and the resultant phenotypes evaluated after transfection into DELTAldnt2 parasites. Whereas an R393K mutant retained transporter activity similar to that of wild type LdNT2, the R393L, D389E, and D389N mutations resulted in dramatic losses of transport capability. Tagging the wild type and mutant ldnt2 proteins with green fluorescent protein demonstrated that the D389N and D389E mutants targeted properly to the parasite cell surface and flagellum, whereas the expression of R393L at the cell surface was profoundly compromised. To test whether Asp389 and Arg393 interact, a series of mutants was generated, D389R/R393R, D389D/R393D, and D389R/R393D, within the green fluorescent protein-tagged LdNT2 construct. Although all of these ldnt2 mutants were transport-deficient, D389R/R393D localized properly to the plasma membrane, while neither D389R/R393R nor D389D/R393D could be detected. Moreover, a transport-incompetent D389N/R393N double ldnt2 mutant also localized to the parasite membrane, whereas a D389L/R393L ldnt2 mutant did not, suggesting that an interaction between residues 389 and 393 may be involved in LdNT2 membrane targeting. These studies establish genetically that Asp389 is critical for optimal transporter function and that a positively charged or polar residue at Arg393 is essential for proper expression of LdNT2 at the plasma membrane.

7/7/4

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16843072 BIOSIS NO.: 200200436583  
Elimination of P1 arginine 393 interaction with underlying glutamic acid 255 partially activates antithrombin III for thrombin inhibition but not factor Xa inhibition

AUTHOR: Jairajpuri Mohamad Aman; Lu Aiqin; Bock Susan C (Reprint)  
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JOURNAL: Journal of Biological Chemistry 277 (27): p24460-24465 July 5, 2002 2002  
MEDIUM: print  
ISSN: 0021-9258  
DOCUMENT TYPE: Article

X

RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: The mechanism for heparin activation of antithrombin III has been postulated to involve disruption of interactions between its reactive loop P1 residue and Glu255 on the underlying protein surface. To test this hypothesis, the potential P1-constraining **Arg393**-Glu255 hydrogen bond and ionic interactions were eliminated by converting Glu255 to alanine. E255A and wild-type ATIIIs have identical reactive loop sequences (including the P1 and P14 residues), but differ in that Glu255-mediated, P1-constraining interactions with the underlying surface cannot form in the mutant. Relative to its wild-type parent, E255A had a 5-fold higher affinity for heparin and pentasaccharide. In the absence of cofactor, E255A exhibited a 5-fold activation of thrombin inhibition but no activation of factor Xa inhibition. Pentasaccharide addition elicited no further activation of thrombin inhibition but increased the factor Xa inhibition rate 100-fold. E255A heparin-dependent thrombin and factor Xa inhibition rates were 1000- and 2-fold faster, respectively, than pentasaccharide-catalyzed rates. Although "approximation" is the predominant factor in heparin activation of ATIII thrombin inhibition, and removal of the P1 constraint plays a distinct but minor role, the primary determinant for activation of factor Xa inhibition is the pentasaccharide-induced conformational change, with approximation making a further minor contribution, and removal of the P1 constraint playing no role at all.

7/7/5

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16218407 BIOSIS NO.: 200100390246

Structure-function analysis of the active site tunnel of yeast RNA triphosphatase

AUTHOR: Bisailon Martin; Shuman Stewart (Reprint)

AUTHOR ADDRESS: Molecular Biology Program, Sloan-Kettering Institute, New York, NY, 10021, USA\*\*USA

JOURNAL: Journal of Biological Chemistry 276 (20): p17261-17266 May 18, 2001 2001

MEDIUM: print

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Cet1, the RNA triphosphatase component of the yeast mRNA capping apparatus, catalyzes metal-dependent gamma phosphate hydrolysis within the hydrophilic interior of a topologically closed 8-strand beta barrel (the "triphosphate tunnel"). We used structure-guided alanine scanning to identify 6 side chains within the triphosphate tunnel that are essential for phosphohydrolase activity in vitro and in vivo: **Arg393**, Glu433, Arg458, Arg469, Asp471 and Thr473. Alanine substitutions at two positions, Asp377 and Lys409, resulted in partial catalytic defects and a thermosensitive growth phenotype. Structure-function relationships were clarified by introducing conservative substitutions. Five residues were found to be nonessential: Lys309, Ser395, Asp397, Lys427, Asn431, and Lys474. The present findings, together with earlier mutational analyses,

reveal an unusually complex active site in which 15 individual side chains in the tunnel cavity are important for catalysis, and each of the 8 strands of the beta barrel contributes at least one functional constituent. The active site residues fall into three classes: (i) those that participate directly in catalysis via coordination of the gamma phosphate or the metal; (ii) those that make critical water-mediated contacts with the gamma phosphate or the metal; and (iii) those that function indirectly via interactions with other essential side chains or by stabilization of the tunnel structure.

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Set	Items	Description
S1	8872	(ANTI()THROMBIN()III) OR (ANTITHROMBIN()III) OR ATIII
S2	291	(RESISTANCE) AND S1
S3	0	S2 AND P3
S4	0	S2 AND CATHEPSIN
S5	1	S2 AND ELASTASE
S6	0	S2 AND ARG393
S7	18	ARG393

? s s1 and p3

8872 S1

9539 P3

S8 7 S1 AND P3

? t s8/6/1-7

8/6/1

11963114 BIOSIS NO.: 199396127530

Conversion of glutamic acid-192 to glutamine in activated protein C changes the substrate specificity and increases reactivity toward macromolecular inhibitors

1993

8/6/2

11848603 BIOSIS NO.: 199396013019

Dissociation of heparin-dependent thrombin and Factor Xa inhibitory activities of %%antithrombin%%-%%III%% by mutations in the reactive site

1993

8/6/3

11721578 BIOSIS NO.: 199395023844

The role of the COOH-terminal region of %%antithrombin%% %%III%%: Evidence that the COOH terminal region of the inhibitor enhances the reactivity of thrombin and factor Xa with the inhibitor

1992

8/6/4

10825933 BIOSIS NO.: 199192071704

THROMBIN GLU-39 RESTRICTS THE P'3 SPECIFICITY TO NONACIDIC RESIDUES

1991

8/6/5

10310690 BIOSIS NO.: 199090095169

ALTERATION OF SERPIN SPECIFICITY BY A PROTEIN COFACTOR VITRONECTIN ENDOWS  
PLASMINOGEN ACTIVATOR INHIBITOR 1 WITH THROMBIN INHIBITORY PROPERTIES  
1990

8/6/6  
09285146 BIOSIS NO.: 198886125067  
HUMAN CYTOTOXIC LYMPHOCYTE TRYPTASE ITS PURIFICATION FROM GRANULES AND THE  
CHARACTERIZATION OF INHIBITOR AND SUBSTRATE SPECIFICITY  
1988

8/6/7  
08681357 BIOSIS NO.: 198784035506  
ALTERED SPECIFICITIES OF GENETICALLY ENGINEERED ALPHA-1 ANTITRYPSIN  
VARIANTS  
1986  
? ds

Set	Items	Description
S1	8872	(ANTI()THROMBIN()III) OR (ANTITHROMBIN()III) OR ATIII
S2	291	(RESISTANCE) AND S1
S3	0	S2 AND P3
S4	0	S2 AND CATHEPSIN
S5	1	S2 AND ELASTASE
S6	0	S2 AND ARG393
S7	18	ARG393
S8	7	S1 AND P3

? t s8/7/1-7

8/7/1  
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11963114 BIOSIS NO.: 199396127530  
Conversion of glutamic acid-192 to glutamine in activated protein C changes  
the substrate specificity and increases reactivity toward macromolecular  
inhibitors  
AUTHOR: Rezaie Alireza R; Esmon Charles T (Reprint)  
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JOURNAL: Journal of Biological Chemistry 268 (27): p19943-19948 1993  
ISSN: 0021-9258  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Protein C is a vitamin K-dependent serine protease zymogen that  
upon activation inhibits the coagulation cascade by inactivating factors  
Va and VIIla. In an attempt to improve the anticoagulant activity of  
activated protein C (APC), we have prepared a mutant of protein C in  
mammalian cells in which Glu at position 192 (chymotrypsin numbering  
system) has been replaced with Gln (PC E192Q). Our strategy is based on  
the observation that the same substitution in thrombin improves the  
catalytic activity toward natural and synthetic substrates that contain  
Asp residues at %P3% and %P3%'. Since factor Va also has an Asp  
at position %P3% in the APC cleavage site of the factor Va heavy



chain, we hypothesized that APC E192Q would inactivate factor Va more rapidly than wild type APC. The mutant inactivated factor Va approximately 2-3-fold faster than wild type. In plasma the mutant exhibited slightly less anticoagulant activity than wild type enzyme. Further characterization revealed that APC E192Q is inhibited 280 times faster than APC by alpha-1-antitrypsin (K-2 = 2.8 times 10<sup>-3</sup> M<sup>-1</sup> S<sup>-1</sup> versus 10 M<sup>-1</sup> S<sup>-1</sup>), and unlike APC, APC E192Q is inhibited by antithrombin in the presence of heparin (K-2 = 1.17 times 10<sup>-3</sup> M<sup>-1</sup> S<sup>-1</sup>) and absence of heparin (K-2 = 57 M<sup>-1</sup> S<sup>-1</sup>). Ca<sup>2+</sup> increased K-2 more than 4-fold with or without heparin. Unlike wild type APC, APC E192Q was effectively inhibited by pancreatic trypsin inhibitor (K-i = 10.6 +/- 0.26 nM) and tissue factor pathway inhibitor (58 +/- 5 nM). Like factor Xa, APC E192Q rapidly processed factor IX to factor IX-alpha. These observations suggest that even though Glu at position 192 is not an optimal residue for catalyzing factor Va inactivation, it is an evolutionary adaptation to slow inhibition by plasma protease inhibitors.

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11848603 BIOSIS NO.: 199396013019

Dissociation of heparin-dependent thrombin and Factor Xa inhibitory activities of antithrombin-III by mutations in the reactive site

AUTHOR: Theunissen Henri J M (Reprint); Dijkema Rein; Grootenhuis Peter D J ; Swinkels Joop C; De Poorter Tom L; Carati Peter; Visser Arie

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JOURNAL: Journal of Biological Chemistry 268 (12): p9035-9040 1993

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Antithrombin-III (AT-III) is a heparin-dependent inhibitor of thrombin and Factor Xa, two serine proteases that are crucial for blood coagulation. In order to assess whether it would be possible to target AT-III only towards Factor Xa, we replaced parts of the reactive site, or P region, of AT-III by sequences present in prothrombin, a substrate of Factor Xa in the coagulation cascade. We show that replacement of the P3 to P3' region generates the hypothesized phenotype. In fact, point mutation of the P1' site from Ser (present in AT-III) to Ile (present in prothrombin) is sufficient to dissociate heparin-dependent thrombin and Factor Xa inhibitory activities. Interestingly, a combined mutation at P3 and P3' brings about the same dissociation. We show that besides Ile, other amino acids at P1' can lead to the dissociation in inhibitory activity. Amino acids with small side chains (Gly, Ser, Ala, and Thr) have only a marginal effect on the inhibitory activity against either protease. However, larger residues at the P1' position abolish the heparin-dependent antithrombin activity, whereas the heparin-dependent anti-Factor Xa activity is not at all or only moderately affected. These results can be rationalized by a comparison of the x-ray structure and a three-dimensional model of the S1' binding pockets of thrombin and Factor

Xa, respectively. It appears that the S1' pocket of Factor Xa leaves much more space for the P1' residue of AT-III than the S1' pocket of thrombin.

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11721578 BIOSIS NO.: 199395023844

The role of the COOH-terminal region of antithrombin III:

Evidence that the COOH terminal region of the inhibitor enhances the reactivity of thrombin and factor Xa with the inhibitor

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JOURNAL: Journal of Biological Chemistry 267 (31): p22224-22229 1992

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: To elucidate the role of the COOH-terminal region of antithrombin III, we studied the effects of synthetic peptides corresponding to its sequence on the amidolytic and proteolytic activities of thrombin and Factor Xa in the presence or absence of the inhibitor, antithrombin III. The peptides ANRPFLVFI and IIFMGRVANP corresponding to residues Ala-404 to Ile-412 and Ile-420 to Pro-429, respectively, blocked the inhibition by antithrombin III. The effect of IIFMGRVANP was reduced in the presence of heparin. Both peptides at a concentration of 1 mM blocked complex formation between antithrombin III and thrombin or Factor Xa. The two peptides, particularly IIFMGRVANP, directly enhanced the amidolytic activity of thrombin and Factor Xa on the synthetic substrate Boc-Ala-Gly-Arg-MCA (where Bos is t-butoxycarbonyl and MCA is 4-methylcoumarin), which corresponds to residues P3-P1 of the reactive site of antithrombin III, and also on other substrates due to increased V-max. IIFMGRVANP also shortened the thrombin-induced fibrinogen clotting time, whereas ANRPFLVFI inhibited the thrombin-catalyzed activation of protein C both in the presence and absence of thrombomodulin. The direct effect of ANRPFLVFI and IIFMGRVANP on thrombin was confirmed by enhancement of the incorporation of dansylarginine-N-(3-ethyl-1,5-pentanedyl)amide into thrombin. These findings suggest that the COOH-terminal region of antithrombin III interacts with thrombin and Factor Xa to increase the reactivity of the enzyme, which may enhance acyl-bond formation between the inhibitor and the enzyme.

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10825933 BIOSIS NO.: 199192071704

THROMBIN GLU-39 RESTRICTS THE P'3 SPECIFICITY TO NONACIDIC RESIDUES

AUTHOR: LE BONNIEC B F (Reprint); MACGILLIVRAY R T A; ESMON C T

AUTHOR ADDRESS: HOWARD HUGHES MED INST, OKLAHOMA MED RES FOUNDATION, 825 NE 13, OKLAHOMA CITY, OKLAHOMA 73104, USA\*\*USA

JOURNAL: Journal of Biological Chemistry 266 (21): p13796-13803 1991  
ISSN: 0021-9258  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: ENGLISH

ABSTRACT: Residue 39 of serine proteases neighbors positions P'2 to P'4 of the substrate. When Glu-39 of thrombin is replaced with Lys, the resultant enzyme (E39K) retains similar P1, P2, and  $^{P3}$  specificities but has altered P'3 and/or P'4 specificities. These conclusions are based on analysis of both p-nitroanilide and synthetic peptide hydrolysis. The activity of E39K is nearly normal toward 17 p-nitroanilide substrates. In peptide substrates, an acidic residue at either the  $^{P3}$  or P'3 position reduces the rate of cleavage by thrombin. A single substitution of Asp with Gly in either the  $^{P3}$  or P'3 position of a peptide corresponding to the P7-P'5 residues of protein C increases the rate of cleavage by thrombin 2-3-fold. Replacement of both Asp residues with Gly increases the rate of cleavage 30-fold. With E39K, the inhibitory effect of Asp in  $^{P3}$  remains unchanged, but Asp in the P'3 site is no longer inhibitory. Significant differences in the catalytic activity of E39K are also seen with respect to protein C activation. In the absence of thrombomodulin, E39K activates protein C 2.2 times faster than thrombin. In the presence of thrombomodulin, the rate of protein C activation is similar for E39K and thrombin. The second order rate constant of inhibition by  $^{antithrombin}$   $^{III}$ , whereas P'4 is a Glu, is slightly increased (1.4-fold). The clotting activity is reduced 2.4-fold due to a lower rate of fibrinopeptides A and B release where P'3 is Arg. These data show that the P'3 position is a determinant of thrombin specificity and suggest that thrombomodulin may function in part by the alleviating the inhibitory effects that may arise from the proximity of the Asp in P'3 of protein C with Glu-39 of thrombin.

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10310690 BIOSIS NO.: 199090095169  
ALTERATION OF SERPIN SPECIFICITY BY A PROTEIN COFACTOR VITRONECTIN ENDOWS  
PLASMINOGEN ACTIVATOR INHIBITOR 1 WITH THROMBIN INHIBITORY PROPERTIES  
AUTHOR: EHRLICH H J (Reprint); GEBBINK R K; KEIJERS J; LINDERS M; PREISSNER  
K T; PANNEKOEK H  
AUTHOR ADDRESS: DEP MOL BIOL, CENTRAL LAB NETHERLANDS RED CROSS BLOOD  
TRANSFUSION SERVICE, PLESMANLAAN 125, 1066 CX AMSTERDAM, NETHERLANDS\*\*  
NETHERLANDS  
JOURNAL: Journal of Biological Chemistry 265 (22): p13029-13035 1990  
ISSN: 0021-9258  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: ENGLISH

ABSTRACT: Serine protease inhibitors ("serpins") are highly homologous proteins which inhibit selected "target" serine proteases by acting as a pseudo-substrate. Their specificity is primarily determined by the amino acid sequence around the carboxyl-terminally located reactive center (P1-P1'). In addition, the association rate constant between a serpin and

a serine protease can be dramatically increased by non-protein cofactors, such as heparin in the case of thrombin inhibition by ~~antithrombin~~ ~~III~~. In an attempt to alter the specificity of PAI-1 from an inhibitor of the fibrinolytic system to an inhibitor of coagulation, we replaced P1-P1' or ~~P3~~ through ~~P3~~' or the reactive center of PAI-1 by the corresponding residues of ~~antithrombin~~ ~~III~~ and ~~assessed whether the mutant proteins, purified from lysates of transformed Escherichia coli cells, had acquired thrombin inhibitory properties.~~ The experiments were performed in the presence and absence of vitronectin, a multifunctional protein which has been shown to bind PAI-1 in plasma and in the matrix of endothelial cells. The second-order rate constants for t-PA inhibition of "wild-type" PAI-1 and PAI P1-P1' ~~ATIII~~, irrespective of the presence of vitronectin, were similar, whereas replacing ~~P3~~-~~P3~~' resulted in a 40-fold decrease of the second-order rate constant towards t-PA, again independent of vitronectin. In the absence of vitronectin, reactivity of PAI-1 and its "~~antithrombin~~ ~~III~~-like" variants towards thrombin was slow; however, PAI-1 ~~P3~~-~~P3~~' ~~ATIII~~ had a 10-fold higher  $k_1$  than wild-type PAI-1 (1.3 .times. 10<sup>4</sup> M<sup>-1</sup> s<sup>-1</sup> versus 1.1 .times. 10<sup>3</sup> M<sup>-1</sup> s<sup>-1</sup>). In contrast, in the presence of vitronectin, PAI-1 and even more rapidly PAI-1 ~~P3~~-~~P3~~' ~~ATIII~~ were found to be effective thrombin inhibitors, with  $k_1$  values of 2.2 .times. 10<sup>5</sup> M<sup>-1</sup> s<sup>-1</sup> and 1.8 .times. 10<sup>6</sup> M<sup>-1</sup> s<sup>-1</sup>, respectively. Thus, in the presence of vitronectin, PAI-1 ~~P3~~-~~P3~~' ~~ATIII~~ displays a 3-fold higher  $k_1$  with thrombin than with t-PA. It is shown that vitronectin enhances, in a dose-dependent manner, the formation of sodium dodecyl sulfate-resistant complexes between PAI-1 or mutants thereof and thrombin. Therefore, vitronectin is the first protein described to function as a cofactor for serpin specificity. PAI-1 is proposed to be a versatile inhibitor which, in the presence of vitronectin, can modulate both coagulation and fibrinolysis.

8/7/6

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09285146 BIOSIS NO.: 198886125067

HUMAN CYTOTOXIC LYMPHOCYTE TRYPTASE ITS PURIFICATION FROM GRANULES AND THE CHARACTERIZATION OF INHIBITOR AND SUBSTRATE SPECIFICITY

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JOURNAL: Journal of Biological Chemistry 263 (26): p13215-13222 1988

ISSN: 0021-9258

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

ABSTRACT: A trypsin-like enzyme (tryptase) has been purified to homogeneity from the granules of a human cytolytic lymphocyte (CTL) line, Q31, by a three-step procedure. By including 0.3% (v/v) Triton X-100 and 1 mg/ml heparin in purification buffers, near total yields of tryptase activity were obtained during the purification. The enzyme, referred to as Q31 tryptase, migrated in polyacrylamide gels with sodium dodecyl sulfate at a position corresponding to 28 kDa with and to 45 kDa without 2-mercaptoethanol. It had an amino-terminal sequence identical to a

previously reported human CTL tryptase at 20 of 22 positions identified. It hydrolyzed N.alpha.-carbobenzyloxy-L-lysyl-thiobenzyl ester (BLT), and this BLT esterase activity was most efficient at slightly alkaline pH and was relatively more active near neutral pH than mouse CTL tryptase. Human .alpha.1-protease inhibitor, human %antithrombin% %III%, phenylmethanesulfonyl fluoride, and p-aminobenzamidine inhibited the Q31 tryptase. The inhibition by human %antithrombin% %III% was rapid enough to be of physiological significance. A survey of oligopeptide p-nitroanilides found that the best substrate for human Q31 tryptase is H-D-(.epsilon.-carbobenzyloxy)Lys-L-Pro-L-Arg-p-nitroanilide. The Q31 tryptase appears to have broad specificity for amino acid residues at P2 and %P3%, i.e. at 2 and 3 residues amino-terminal to the scissile bond.

8/7/7

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08681357 BIOSIS NO.: 198784035506

ALTERED SPECIFICITIES OF GENETICALLY ENGINEERED ALPHA-1 ANTITRYPSIN  
VARIANTS

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JOURNAL: Protein Engineering 1 (1): p29-36 1986

ISSN: 0269-2139

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LANGUAGE: ENGLISH

ABSTRACT: Seven active site variants of human .alpha.1-antitrypsin (.alpha.1AT) were produced in Escherichia coli following site-specific mutagenesis of the .alpha.1AT complementary DNA. .alpha.1AT (Ala358), .alpha.1AT (Ile358) and .alpha.1AT (Val358) were efficient inhibitors of both neutrophil and pancreatic elastases, but not of cathepsin G. .alpha.1AT (Ala356, Val358) and .alpha.1AT (Phe358) specifically inhibited pancreatic elastase and cathepsin G respectively. The most potent inhibitor of neutrophil elastase was .alpha.1AT (Leu358), which also proved to be effective against cathepsin G. The .alpha.1AT (Arg358) variant inactivated thrombin with kinetics similar to %antithrombin% %III% in the presence of heparin. Electrophoretic analysis showed that SDS-stable high mol. wt complexes were formed between the mutant inhibitors and the cognate proteases in each case. These data indicate that effective inhibition occurs have .alpha.1AT P1 residue (position 358) corresponds to the primary specificity of the target protease. Moreover, alteration of the %P3% residue (position 356) can further modify the reactivity of the inhibitor. Two of the variants have therapeutic potential: .alpha.1AT (Leu358) may be more useful than plasma .alpha.1AT in the treatment of destructive lung disorders and .alpha.1AT (Arg358) could be effective in the control of thrombosis.

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Set	Items	Description
S1	8872	(ANTI()THROMBIN()III) OR (ANTITHROMBIN()III) OR ATIII
S2	291	(RESISTANCE) AND S1

S3 0 S2 AND P3  
 S4 0 S2 AND CATHEPSIN  
 S5 1 S2 AND ELASTASE  
 S6 0 S2 AND ARG393  
 S7 18 ARG393  
 S8 7 S1 AND P3

? s1 and mutat?

4099285 1

366227 MUTAT?

S9 118526 1 AND MUTAT?

? s s1 and mutat?

8872 S1

366227 MUTAT?

S10 433 S1 AND MUTAT?

? s s2 and mutat?

291 S2

366227 MUTAT?

S11 94 S2 AND MUTAT?

? t s11/7/1-94

11/7/1

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0019597894 BIOSIS NO.: 200700257635

Outcomes during and after pregnancy in patients with primary hypercoagulable states.

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JOURNAL: Blood 108 (11, Part 1): p266A NOV 16 2006 2006

CONFERENCE/MEETING: 48th Annual Meeting of the

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SPONSOR: Amer Soc Hematol

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LANGUAGE: English

ABSTRACT: Pregnant women with primary hypercoagulable states have an increased risk of recurrent fetal loss, fetal growth retardation, preeclampsia, and placental abruption, as well as thromboembolism in both the antepartum and postpartum periods. Conditions that have been associated with adverse pregnancy outcomes include inherited gene mutation disorders such as Factor V Leiden G1691A (FVL); prothrombin gene mutation G20210A (PGM); hyperhomocysteinemia with C677T mutation (MTHFR); deficiencies of protein S (PS), protein C (PC), antithrombin III (ATIII); and anticardiolipin antibodies/lupus anticoagulants (LA). Screening by obstetricians for these disorders has led to an increase in diagnosis yet there are no established guidelines and therapeutic interventions are variable. A retrospective chart review was conducted on 59 women and 197 pregnancies (1-12 per pt) in whom primary hypercoagulable state was diagnosed: FVL (n=), PGM (n= 11), MTHFR (n=3), ATIII (n=2), PC (n=1), PS (n=8), LA (n=10), and those with more than one thrombophilic risk (TR) (n=12) or lupus (n=2). Of the 197 pregnancies, only 106 (54%) were carried to term in 50 pts (85%). Of the remaining 91 pregnancies, there were 16

terminations, 5 ectopic pregnancies and 4 preterm live births. 66 fetal losses occurred: 45 in the first trimester (26 with single TR/19 with > 1 TR), 19 in the 2nd-3rd trimester (14 with single TR/ 5 with > 1 TR) and 2 unknown. See Table for risk of fetal loss by class of hypercoagulable state. Venous thromboembolism occurred in 8/106 (8%) of term pregnancies, including 5 postpartum. Of women with previous fetal losses, management with anticoagulation (A/C) subsequently was utilized in 20 pregnancies: 9 low molecular weight heparin (LMWH), 6 LMWH+aspirin (ASA), 3 heparin (H), 1 ASA, and 1 H+ASA. 18/20(90%) of these pregnancies resulted in live term births; 1 loss due to intracranial hemorrhage at 27 weeks in a patient on L+ASA. Compared to 146 pregnancies untreated with A/C, successful completion of pregnancy was significantly greater on A/C, 90% vs. 58% (p=0.006). Conclusions: Fetal losses secondary to TR occurred in both the first and late trimesters in high proportion of pregnancies in women with hypercoagulable states. Outcomes may be improved with the use of A/C therapy. [GRAPHICS]ication or therapy duration. Nor was there significant correlation between any of the measures of aspirin resistance we studied. In this initial prevalence study of a clinically diverse group of pediatric patients, laboratory evidence of aspirin resistance was not commonly encountered, despite our utilization of a broad panel of assays previously reported to identify aspirin resistance in adults. The prevalence of aspirin resistance in children thus appears low, and possibly less than that in adults. However, for the minority of pediatric patients who demonstrate laboratory evidence of aspirin resistance, this finding may hold clinical relevance; clinical follow-up of this cohort is ongoing. Finally, the lack of correlation we observed between assays previously linked to adverse clinical outcomes in patients taking aspirin supports that multiple molecular mechanisms contribute to the clinical phenotype of aspirin treatment failure.

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0019489054 BIOSIS NO.: 200700148795

Assessing thrombosis risk in patients with idiopathic, diabetic, and postsurgical gastroparesis

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JOURNAL: Advances in Therapy 23 (5): p750-768 SEP-OCT 2006 2006

ISSN: 0741-238X

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Patients with severe gastrointestinal motility disorders are often found to have intravenous access clots or deep venous thrombosis. It has previously been reported that many patients who have intravenous access thrombosis have concomitant thrombotic risk factors. In this study, the goal was to determine the underlying prevalence of hypercoagulable risk in a series of patients with documented gastroparesis. Investigators studied 62 consecutive patients (52 female;

mean age, 42 y) who had symptoms of gastroparesis. All patients were evaluated for placement of a gastric neural stimulation device, or they had had one placed previously. Patients underwent a hematologic interview and standardized coagulation measures of thrombotic risk. Laboratory studies measured acquired elevations of Factor VII, Factor VIII, fibrinogen, lupus anticoagulant panel, antiphospholipid antibody panel, homocysteine (in the setting of kidney disease), and activated protein %resistance%. investigators also measured congenital factors: Factor VIII (with C-reactive protein levels), %antithrombin% %III%, protein C, protein S (total and free), Factor II %mutation%, Factor V Leiden, methylenetetrahydrofolate reductase, and homocysteine. Fifty-five patients (89%) were found to have detectable hypercoagulable risk factors. Twenty-five of the 62 patients (40%) had a documented history of abnormal clotting, including deep venous thrombosis, intravenous access thrombosis, and pulmonary embolism. All patients with a previous history of thrombosis had detectable clotting abnormalities. Of 56 patients, 40 (71%) had hypercoagulability and did not have diabetes ( $P=.036$ ), and 20 (36%) had hypercoagulability and no known history of infection. However, this value was not statistically significant when infection and hypercoagulability were compared ( $P=.408$ ). A high prevalence of acquired and congenital hypercoagulable defects has been observed in patients with gastroparesis, which may predispose them to arterial and venous clots. This unique finding warrants consideration of coagulation evaluation in patients with severe gastroparesis, especially when these patients are placed in high-risk thrombophilic situations, such as hospitalization, prolonged intravenous access, and surgery.

11/7/3

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0019462722 BIOSIS NO.: 200700122463

Elevated anticardiolipin antibodies are an independent risk factor for neurological complications in carotid stenting

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JOURNAL: Circulation 114 (18, Suppl. S): p396 OCT 31 2006 2006

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LANGUAGE: English

ABSTRACT: Background and Purpose - Carotid stenting (CS) has become a therapeutic alternative to endarterectomy in the treatment of high-grade internal carotid artery stenosis. Despite the development of cerebral protection devices periinterventional thromboembolism and consecutive neurological deficit (PND) remain the major risk factor for the procedure. Next to previously identified risk factors we prospectively studied the potential role of thrombophilic conditions in patients undergoing CS. Methods - Anticardiolipin antibodies (ACL, IgG isotype),



antithrombin, and protein C and S levels were quantitated in patients with high-grade (> 70%) carotid artery stenosis before CS. In addition, activated protein C resistance (APC-R) was measured followed by factor V Leiden mutation analysis in patients with low APC-R ratio. Occurrence of periprocedural neurological deficit within 48 hours after the procedure was recorded. Logistic regression analysis was performed to test for the influence of thrombophilic conditions, demographic factors and lesion characteristics on PND. Results - A total of 232 patients with symptomatic (n=59) or asymptomatic (n=173) cerebrovascular disease, who underwent unprotected (n=135) or protected (n=95) CS, were included in the study. PND occurred in 19 patients (8.2%) with a similar cardiovascular risk profile compared to the non-PND group. In 4 (36%) out of 11 patients with elevated ACL (> 15 Units/ml) neurological ischemic complications were observed. Two identified variables were independently associated with PND: lesion length > 11.2mm (OR 6.3, 95% CI 1.3 to 30) and heightened ACL (OR 7.1, 95% CI 1.5-32.4). Conclusion - A thrombophilic condition due to elevation of anticardiolipin antibodies increases the risk of periinterventional neurological complications during CS. In addition, we confirm previous data on higher PND risk dependent on lesion length.

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19314234 BIOSIS NO.: 200600659629

Methylenetetrahydrofolate reductase C677T gene mutation prevalence and its contribution with other thrombophilic factors in pediatric cases with portal vein thrombosis

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JOURNAL: Liver International 26 (Suppl. 1): p113 OCT 2006 2006

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11/7/5

DIALOG(R)File 5:Biosis Previews(R)

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19221515 BIOSIS NO.: 200600566910

Inherited and acquired thrombophilia: Pregnancy outcome and treatment

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JOURNAL: Reproductive Toxicology 22 (2, Sp. Iss. SI): p227-233 AUG 2006 2006

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ABSTRACT: Maternal thrombophilias increases the risk of an adverse pregnancy outcome. An extensive literature review highlights the role of inherited and acquired thrombophilic disorders in spontaneous abortion, both early and late, recurrent or isolate, in intrauterine growth retardation, in placenta abruption, in pre-eclampsia and in venous thromboembolism. We have particularly focused attention on the following factors: antithrombin (ATIII), proteins C (PC) and S (PS) deficiencies, genetic mutations particularly factor V Leiden (FVL), prothrombin gene G20210A (PTM) and the thermolabile variant of the methylene tetrahydrofolate reductase C677T (MTHFR) gene, lupus anticoagulant (LAC) and anticardiolipin antibodies, VIIIc factor, hyperhomocysteinemia and acquired activated protein C resistance. Appropriate treatment can improve pregnancy outcome without teratogenic effects. (c) 2006 Elsevier Inc. All rights reserved.

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19031955 BIOSIS NO.: 200600377350

Thrombophilic screening in healthy donors treated with recombinant-human granulocyte-colony stimulating factor for mobilisation of peripheral blood stem cells

AUTHOR: Martino M (Reprint); Moscato T; Console G; Irrera G; Messina G; Massara E; Pratico G; Quartarone E; Mammi C; Luise F; Piromalli A; Iacopino P

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JOURNAL: Bone Marrow Transplantation 37 (Suppl. 1): pS336 MAR 2006 2006

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DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

11/7/7

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18962109 BIOSIS NO.: 200600307504

Lack of association between inherited thrombophilic risk factors and idiopathic sudden sensorineural hearing loss in Italian patients

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JOURNAL: Annals of Otology Rhinology & Laryngology 115 (3): p195-200 MAR  
2006 2006  
ISSN: 0003-4894  
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LANGUAGE: English

ABSTRACT: Objectives: We investigated the presence of congenital thrombophilic risk factors in a population of consecutive Italian patients affected by idiopathic sudden sensorineural hearing loss (SSNHL). Methods: We investigated 48 patients with idiopathic SSNHL for the presence of congenital thrombophilic risk factors. The factor V Leiden G1691A, the prothrombin G20210A allele, and methylenetetrahydrofolate reductase (MTHFR) C677T genotypes were investigated. Allele frequencies and genotype distribution of all factors found in patients were compared to those of 48 healthy subjects of the same ethnic background by chi(2) and odds-ratio analysis. Odds ratios and 95% confidence intervals were calculated for allele and genotype frequencies of all thrombophilia variants. Statistical significance was accepted with a p value of less than .05. We also performed the following blood tests: hemacytometric analysis including platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, erythrocyte sedimentation rate, C-reactive protein, protein S, protein C, %antithrombin%, %III%, and activated protein C %resistance%. Results: In our series, we did not find an association between SSNHL and abnormal levels of %antithrombin%, %III%, protein C, protein S, D-dimer, or fibrinogen; activated protein C %resistance%; or factor V G1691A, prothrombin G20210A, or MTHFR C677T %mutations%. Conclusions: At present, the few studies regarding genetic polymorphisms of congenital thrombophilic factors in SSNHL are not conclusive. According to our data, factor V G1691A, prothrombin G20210A, and MTHFR C677T variants should be not considered risk factors for SSNHL. Further large prospective studies are needed to provide currently lacking information and to improve our knowledge in the field before we recommend the determination of genetic polymorphism in SSNHL as routine practice.

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18838592 BIOSIS NO.: 200600183987  
High prevalence of hyperhomocysteine in retinal vein occlusion.  
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JOURNAL: Blood 106 (11, Part 1): p462A-463A NOV 16 2005 2005  
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American-Society-of-Hematology Atlanta, GA, USA December 10 -13, 2005;  
20051210  
SPONSOR: Amer Soc Hematol  
ISSN: 0006-4971  
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RECORD TYPE: Abstract

LANGUAGE: English

**ABSTRACT:** Retinal vein occlusion (RVO) is a common cause of blindness. Despite its clinical relevance, the role of inherited thrombophilia in RVO is controversial (Janssen MC et al., Thrombosis and Haemostasis 2005; 93). Although many authors consider more important the role of anatomical conditions of lamina cribrosa rather than hypercoagulability in pathogenesis of this disease, the use of antithrombotic drugs for treatment of RVO is widespread (Prisco D et al., Pathophysiology of Haemostasis and Thrombosis 2002;32). To evaluate the most important thrombotic risk factors, we collected the data of 80 consecutive patients referred to our Centers for a RVO confirmed by fluoroangiography. Our cohort includes 39 women and 41 men with median age of 66 years; we observed 42 central retinal vein occlusions (CRVO) and 38 branch retinal vein occlusions (BRVO) from March 2002 to July 2005. We collected the following data about cardiovascular risk factors: the prevalence of arterial hypertension was 47,5% (38/80), dyslipidemia 22.5% (18/80), obesity 7.5% (6/80), diabetes mellitus 10% (8/80). Forty-four patients (55%) demonstrated one or more atherosclerotic risk factors. The prevalence of acquired conditions did not show any statistical difference between CRVO and BRVO patients. Moreover we tested fasting homocysteine in 60 patients detecting hyperhomocysteine (defined as a value of homocysteine above 95 degrees percentile of laboratory control group) in 19 cases (31%). Only one patient showed Lupus Anticoagulant and anticardiolipin antibody positivity. Moreover we registered a CRVO during tamoxifen treatment and another one during hormonal therapy. When we considered venous thrombophilia (hormonal therapy, neoplasia, immobilization, surgery, hyperhomocysteine, LAC) we found 25 patients (31.3%) having one or more acquired thrombotic risk factors. Besides, all patients were tested for: antithrombin, protein C and protein S, activated protein C resistance, factor V Leiden and prothrombin G20210A. We found the presence of genetic thrombophilia in 14 patients (17,5%): nine patients had protein S deficit; five had prothrombin gene mutation and one patient had factor V Leiden and one had factor XII deficit (two patients had multiple defects). Results of our survey confirm that acquired risk factors have a more relevant role than genetic thrombophilia in RVO. To draw a conclusion, extensive screening of genetic thrombophilia is not cost-effective in RVO but detection of plasmatic homocysteine concentration can be useful because high frequency of hyperhomocysteine and the possibility of treatment with vitamin B12 and folic acid. Finally we are surprised to see high frequency of protein S deficit in our cohort. [GRAPHCS]

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18838005 BIOSIS NO.: 200600183400

Assessing the role of continuous activated protein C (APC) expression in murine thrombosis models

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JOURNAL: Blood 106 (11, Part 1): p301A NOV 16 2005 2005

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**ABSTRACT:** The protein C (PC) pathway plays a major role in the interface between coagulation and inflammation. APC has both anticoagulant and anti-inflammatory properties and is the only effective treatment in patients with severe sepsis. However, assessment of APC's therapeutic effect on other complex disease models has been compromised by its short half-life (15 min) and by difficulties in monitoring protein levels. To overcome this limitation we used adeno-associated viral (AAV) vectors encoding the PC zymogen or APC for hepatocyte specific gene expression. For direct APC secretion we introduced an extra cleavage site adjacent to the activation peptide for the intracellular protease PACE/furin. Three dose cohorts of C57Bl/6 mice (n=4-6 per group) were injected for either AAV-APC or AAV-PC. A single vector injection resulted in continuous sustained long-term PC or APC expression without signs of liver toxicity. APC functional activity was restricted to AAV-APC-treated mice in which APC plateau levels of 88 +/- 43, 162 +/- 48, or 263 +/- 64 ng/ml were determined in a dose dependent manner. Further, AAV-APC expression consisted mainly of APC because no PC was detected by a zymogen specific ELISA. Only APC expressing mice presented enhanced anticoagulation as determined by 11 to 41 % prolongation of the aPTT values ( $p < 0.05-0.005$ ) and decreased thrombin/antithrombin complex (TAT) levels (from 30 at baseline to 20, 14, or 12 ng/ml,  $p < 0.05-0.0005$ ). Next, we tested whether APC or PC would provide protection against vascular injury at both micro- and macrocirculation levels of living animals. No thrombus formation was detected in APC expressing mice (n=4) following FeCl<sub>3</sub>-injury of the carotid artery in contrast to uninjected or PC expressing controls (7 thrombi in 7 mice,  $p < 0.01$ ). Anticoagulant efficacy was then evaluated by real-time imaging of thrombus formation following laser induced arteriole injury using widefield intravital microscopy. In AAV-APC treated mice we observed dose dependent anticoagulation: 8 thrombi/12 injury sites in mice expressing similar to 80 ng/ml, 3/10 at similar to 160 ng, and 1/7 at similar to 260 ng/ml APC compared to 42/42 in untreated controls ( $P < 0.001-0.0001$ ). Expression of PC resulted in prevention of thrombus formation only at the highest expression levels of 4000 ng/ml (5/7,  $p < 0.02$ ) but not at 2000 ng/ml (10/10). When these animals were challenged by tail clipping, blood loss was increased only for mice with the highest APC levels by 2-fold ( $p < 0.05$ ). Moreover, at all levels of APC no changes in wound healing rates were observed following punch biopsy. Treatment of homozygous mice for the factor V Leiden (FVL) mutation with the same vector doses (n=3/group) resulted in a similar anticoagulant effect based on the aPTT with 18-27 % prolongation ( $p < 0.05$ ), or based on TAT levels, dropping from 56.9 ng/ml at baseline to 28.1, 12.9, or 8.0 ng/ml ( $p < 0.05-0.0005$ ). This data shows that continuous expression of APC can overcome the inherited proteolytic resistance of FVL to APC. In summary, these results demonstrate that APC levels, within the range already obtained in humans by protein infusion (up to 400 ng/ml), provide antithrombotic activity dependent on the injury and/or vessel size. In our model, human APC levels of 160 ng/ml present effective anticoagulant effect without increasing the risk of bleeding. This strategy ensures easy assessment of

the role of APC in complex disease models at closely defined circulating levels.

11/7/10

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18787126 BIOSIS NO.: 200600132521

The spectrum of hypercoagulable states in minority patients with unexplained thrombosis.

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ABSTRACT: The association of genetic risk factors with hypercoagulable states in minority populations has not been well defined. With an estimated prevalence of anywhere between 2-15% in healthy individuals, activated protein C resistance (APCR/Factor V Leiden) is considered to be the most common risk factor for venous thromboembolism (VTE) in the white population. It has also been postulated that this mutation is extremely rare in non-white populations. The prevalence of the prothrombin gene mutation G20210A in the white population is estimated at 0.7-4%, protein C and S deficiencies at 2% each and antithrombin deficiency at 0.1-0.5% but unknown in Blacks with VTE though case control studies have identified protein C and protein S deficiencies in this population. This study is a retrospective review of all patients with thrombophilia registered at the Hemophilia Treatment Center between 1999-2005. 45/164(27%) of patients with thrombophilia were identified to be from minority groups. Of these minority patients 23/45(51%) had an identifiable primary hypercoagulable state. This group included 7/23(30%) males and 16/23(70%) females. The mean age of the patients was 35 years(range 12-80 years). 4/23(17%) were smokers and only 4/23(17%) had a family history of thrombosis with no documented hypercoagulable states in any family members. The majority of the patients were of African American descent 16/23(69%), 5/23(22%) were Hispanic and 2/23(9%) were Asians. 16/23(69%) of the patients had documented deep venous thrombosis/pulmonary embolus, 1/23(4%) had arterial thrombosis, 3/23(13%) had fetal loss, and 2/23(9%) were asymptomatic. APCR was the most common diagnosis in 8/23(35%) of the patients, followed by antiphospholipid antibody syndrome in 7/23(30%) of the patients. Protein S deficiency was diagnosed in 5/23(22%), hyperhomocysteinemia in 4/23(17%), Protein C deficiency in 1/23(4%), antithrombin deficiency in 1/23(4%), and prothrombin gene mutation in 1/23(4%) of the patients. 4/23(17%) of the patients were found to have two coexisting hypercoagulable diagnoses. Recurrent VTE occurred in 7/23(30%) of the patients. Conclusion: Primary hypercoagulable states are not rare in minorities. In this study, APCR was found to be the most common identified abnormality, followed by

antiphospholipid antibody and protein S deficiency. Similar to the white population, thrombophilia in minorities occurred more commonly in young female patients. Work up for primary hypercoagulable, states should be considered in minority patients with unexplained thrombosis. Further studies are warranted to determine the true prevalence of hypercoagulable states in minority populations.

11/7/11

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18710497 BIOSIS NO.: 200600055892

Is elevated level of soluble endothelial protein C receptor a new risk factor for retinal vein occlusion?

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JOURNAL: IOVS 46 (Suppl. S): p4051 2005 2005

CONFERENCE/MEETING: Annual Meeting of the Association-for-Research-in-Vision-and-Ophthalmology Ft Lauderdale, FL, USA May 01 -05, 2005; 20050501

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ABSTRACT: Purpose: To evaluate the systemic and thrombophilic risk factors involved in retinal vein occlusion (RVO) and to determine whether the elevated level of soluble endothelial protein C receptor (sEPCR) is a risk factor for retinal vein thrombosis. Methods: Fifty-six patients with central RVO (CRVO), 26 patients with branch RVO (BRVO) and 78 otherwise healthy sex- and age-matched subjects who presented with refractive errors, presbyopia, or cataract were enrolled in this study. After a written informed consent, all patients underwent complete ophthalmologic examination. Venous blood samples were taken after an overnight fast of at least 8 hours for the analysis of glucose, lipid profile, lipoprotein (a), homocysteine, activated partial thromboplastin time, fibrinogen, factor VIII, protein C activity, protein S activity, activated protein C resistance, antithrombin activity, lupus anticoagulant, anti-cardiolipin antibody, anti-phospholipid antibody, sEPCR, factor V Leiden mutation, and prothrombin G20210A mutation. Results: Apart from hypertension, glaucoma, lipoprotein (a), homocysteine, and factor VIII, elevated level of sEPCR was found to be a risk factor for CRVO (odds ratio, 1.023; 95% confidence interval, 1.009-1.037; p=0.001) with logistic regression. Patients with CRVO had significantly higher levels of sEPCR than those of BRVO and controls (Mean levels (ng/ml): 144.0 +/- 83.8, 116.8 +/- 65.2, and 103.3 +/- 56.1 respectively; p=0.021). Moreover, 31% of patients with CRVO had levels of sEPCR more than 200 ng/ml, while only 6% and 11% of patients had similar high levels in the control and BRVO groups, respectively. Conclusions: Besides known classical risk factors, elevated level of sEPCR seems to be an important candidate risk factor for especially CRVO.

11/7/12

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18575188 BIOSIS NO.: 200510269688

The factor IXA heparin-binding exosite is a critical cofactor interactive site: Mechanism for antithrombin-independent inhibition of intrinsic tenase by heparin

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JOURNAL: Blood 104 (11, Part 1): p476A-477A NOV 16 2004 2004

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ABSTRACT: Therapeutic heparin concentrations selectively inhibit the intrinsic tenase complex in an antithrombin-independent manner. To define the molecular target and mechanism for this inhibition, recombinant human factor IX (FIX) with alanine substituted for solvent-exposed basic residues (H92, R170, R233, K241) in the protease domain was expressed in HEK 293 cells, activated by FIXa, and characterized with regard to enzymatic activity, heparin affinity, and inhibition by low molecular weight heparin (LMWH). The recombinant FIX proteins were purified to homogeneity by SDS-PAGE analysis and exhibited indistinguishable chromatographic behavior when eluted from a Resource Q column with a calcium gradient. FIX was activated with human FIXa (150:1 molar ratio) at 4 degrees C for 2-6 lit, incubated with anti-FIXa polyclonal antisera crosslinked to Affi-gel, and FIXa active sites were determined by a modified antithrombin titration. These mutations had only modest effects on chromogenic substrate hydrolysis and the kinetics of factor X activation by FIXa. The  $k(\text{cat})/K\text{-M}$  for factor X activation by FIXa-phospholipid (5 nM FIXa, 50  $\mu\text{M}$  PC:PS vesicles, 30% ethylene glycol) was similar for all recombinant proteases except FIXa R233A, which was modestly lower due to a 1.4-fold increase in  $K\text{-M}(\text{app})$ . In a functional binding assay, FIXa H92A and K241A exhibited apparent FIXa-FVIIIa affinity similar to FIXa wild type (WT) ( $K\text{-D}(\text{app}) = 2.2, 1.9, \text{ and } 1.7 \text{ nM}$ , respectively). FIXa R170A had markedly increased FIXa-FVIIIa affinity ( $K\text{-D}(\text{app}) = 0.4 \text{ nM}$ ), and consistent with previous results, dramatically increased coagulant activity (372%) relative to FIXa WT (J. Chang et al. JBC, 1998). FIXa R233A had significantly reduced cofactor affinity ( $K\text{-D}(\text{app}) = 4.4 \text{ nM}$ ) and coagulant activity (59%). FIXa R233A also had reduced ability to stabilize the in vitro half-life of FVIIIa relative to FIXa WT (2-fold faster degradation), even at increased protease concentration. Thus, this mutation disrupts interaction with the A2 domain, suggesting that this critical cofactor interactive site extends from the established c165-170 alpha-helix to the proximal portion of the C-terminus  $\alpha$ -helix on FIXa. Using  $K\text{-D}(\text{app})$  to calculate the concentration of FIXa-FVIIIa, no significant differences in the  $k(\text{cat})/K\text{-M}$  for factor X activation by FIXa-FVIIIa-phospholipid were observed between proteases (1-2 nM FVIIIa, 0.1 nM FIXa, 50  $\mu\text{M}$  PC:PS vesicles). Relative heparin affinity of FIXa was assessed by direct and competition binding to immobilized LMWH detected by surface plasmon resonance. Mutant FIXa (250 nM) demonstrated moderately reduced (H92A,



R170A, K241A) or minimal (R233A) binding to immobilized LMWH, relative to FIXa WT. Solution competition demonstrated that the EC50 for LMWH was increased less than 2-fold for FIXa H92A and K241A, but over 3.5-fold for FIXa R170A, indicating that relative heparin affinity was WT>H92A/K241A>R170A>>R233A. Kinetic analysis of the inhibition of factor X activation by intrinsic tenase demonstrated that relative affinity for LMWH was WT>K241A>H92A> R170A>>R233A, correlating with heparin affinity. Notably, FIXa R233A demonstrated minimal binding to immobilized LMWH, and almost complete resistance to inhibition by LMWH in the intrinsic tenase complex. Thus, LMWH inhibits intrinsic tenase by interacting with the heparin-binding exosite on the FIXa protease domain. The extensive overlap between heparin and FVIIIa interactive sites on the protease domain suggest that oligosaccharide disrupts critical interactions with the cofactor A2 domain.

11/7/13

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18572206 BIOSIS NO.: 200510266706

Lack of association between recurrent pregnancy loss and inherited thrombophilia in hispanic patients from Colombia </PRE >.

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Introduction: Several genetic defects of coagulation factors have been implicated as a possible cause of recurrent pregnancy loss in Caucasians. The role of inherited thrombophilia as a risk factor in populations of Hispanic origin affected with this clinical condition is unknown. To our knowledge, this is the first study conducted to evaluate this genetic predisposition in Hispanics. Objective: To assess association between recurrent pregnancy loss and inherited thrombophilias: factor V G1691A (FV Leiden), prothrombin G20210A (FII G20210A), methylenetetrahydrofolate reductase C677T (MTHFR C677T), activated protein C resistance (APC resistance), and deficiencies of antithrombin (AT-III) and protein C (PC). Patients and methods: This ongoing case-control study investigates a tri-ethnic population of Hispanic origin from Medellin, Colombia. Inherited thrombophilia was studied in 76 recurrent pregnancy loss patients according to Sixth ACCP Consensus Conference on Antithrombotic Therapy (three or more miscarriages, and either second-trimester losses or gestational vascular complications). The control group included 117 healthy women (two or more children, and no more than one miscarriage). Polymorphisms were genotyped by PCR-RFLP. APC resistance and

deficiencies of AT-III, and PC were evaluated using commercial kits (IL Test (TM) APC (TM) %%%Resistance%%% V, Antithrombin (TM), and Proclot (TM)). Sample size of 100 patients and 200 controls was determined to have 80% statistical power to discriminate association. Results: The prevalence of any inherited thrombophilia in this patient cohort was 17%, and 25% in controls (OR 1.16, CI 0.6-2.29). No statistically significant differences in any genetic thrombophilia frequency between patients and healthy controls were observed. FV Leiden and FII G20210A were both positive in one patient and one control (OR 1.55, CI 0-57.5, for both thrombophilic defects). In the patient group 13.2% homozygous carriers with MTHFR 677T were found, as compared to 22.2% among controls (OR 0.53, CI 0.22-1.25). The odds ratio for the association between recurrent pregnancy loss and APC %%%resistance%%% was 0.77 (CI 0.32-4.2). The inheritance of AT-III deficiency or PC deficiency was not associated with recurrent pregnancy loss. AT-III deficiency was not detected in patients and was found in only one control. Furthermore, one patient was defined as PC deficiency carrier while none were found in the control group. Conclusion: Our preliminary results found no association between recurrent pregnancy loss and inherited thrombophilia in this population originated by admixture of Amerinds, Europeans, and Africans, such as the American population denominated Hispanic. Base on our current data analysis, we do not expect to find any association even with the planned larger sample size. This suggests that inherited thrombophilia might not play a main role in Hispanic populations affected with this clinical condition. Given these results, appears to be insufficient evidence to include inherited thrombophilia in the initial evaluation of recurrent pregnancy loss in this population group, and possibly Hispanic patients in America. We suggest it is important to look for other, more common, causes of recurrent miscarriage in the evaluation of this group of patients. These data suggest an important ethnic difference between this population and Caucasians.

11/7/14

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18497755 BIOSIS NO.: 200510192255

Ischemic stroke subtypes and thrombophilia in young and elderly Brazilian stroke patients admitted to a rehabilitation hospital

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ABSTRACT: Background and Purpose - We sought to examine ischemic stroke subtypes and prevalence of thrombophilia in Brazilian stroke patients. Method - A total of 130 consecutive young and 200 elderly stroke patients were studied. Results - Prevalence of thrombophilia was, respectively: protein S deficiency (11.5% versus 5.5%), protein C deficiency (0.76% versus 1%), %%%resistance%%% to activated protein C

(2.3% versus 3.5%), %mutation% in V Leiden factor (1.5% versus 2%), %antithrombin% %III% deficiency (0% versus 0%), lupus anticoagulant (0% versus 0.5%), anticardiolipin antibodies (3% versus 10%; P = 0.01), hyperhomocysteinemia (31.5% versus 53.5%; P = 0.0001), %mutation% of the MTHFR gene in homocigosis (10% versus 5%), and heterocigosis (27.6% versus 41.9%; P = 0.01). Conclusion - Prothrombotic conditions were more frequent in stroke of undetermined cause.

11/7/15

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18496773 BIOSIS NO.: 200510191273

The relationship of the factor v Leiden %mutation% and pregnancy outcomes for mother and fetus

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ABSTRACT: Objective: We sought to estimate the frequency of pregnancy-related thromboembolic events among carriers of the factor V Leiden (FVL) %mutation% without a personal history of thromboembolism, and to evaluate the impact of maternal and fetal FVL %mutation% carriage or other thrombophilias on the risk of adverse outcomes. Methods: Women with a singleton pregnancy and no history of thromboembolism were recruited at 13 clinical centers before 14 weeks of gestation from April 2000 to August 2001. Each was tested for the FVL %mutation%, as was the resultant conceptus after delivery or after miscarriage, when available. The incidence of thromboembolism (primary outcome), and of other adverse outcomes, was compared between FVL %mutation% carriers and noncarriers. We also compared adverse outcomes in a secondary nested carrier-control analysis of FVL %mutation% and other coagulation abnormalities. In this secondary analysis, we defined carriers as women having one or more of the following traits: carrier for FVL %mutation%, protein C deficiency, protein S deficiency, %antithrombin% %III% deficiency, activated protein C %resistance%, or lupus anticoagulant-positive, heterozygous for prothrombin G20210A or homozygous for the 5,10 methylenetetrahydrofolate reductase %mutations%. Carriers of the FVL %mutation% alone (with or without activated protein C %resistance%) were compared with those having one or more other coagulation abnormalities and with controls with no coagulation abnormality. Results: One hundred thirty-four FVL %Mutation% carriers were identified among 4,885 gravidas (2.7%), with both FVL %mutation% status and pregnancy outcomes available. No thromboembolic events occurred among the FVL %mutation% carriers (0%, 95% confidence interval 0-2.7%). Three pulmonary emboli and one deep venous thrombosis occurred (0.081%, 95% confidence interval 0.02-0.21%), all occurring in FVL %mutation% noncarriers. In the nested carrier-control analysis (n = 339), no differences in adverse pregnancy outcomes were observed between FVL %mutation% carriers, carriers of other coagulation

disorders, and controls. Maternal FVL %%%mutation%% carriage was not associated with increased pregnancy loss, preeclampsia, placental abruption, or small for gestational age births. However, fetal FVL %%%mutation%% carriage was associated with more frequent preeclampsia among African-American (15.0%) and Hispanic (12.5%) women than white women (2.6%,  $P = .04$ ), adjusted odds ratio 2.4 (95% confidence interval 1.0-5.2,  $P = .05$ ). Conclusion: Among women with no history of thromboembolism, maternal heterozygous carriage of the FVL %%%mutation%% is associated with a low risk of venous thromboembolism in pregnancy. Neither universal screening for the FVL %%%mutation%%, nor treatment of low-risk carriers during pregnancy is indicated.

11/7/16

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18378844 BIOSIS NO.: 200510073344

Coagulation management of a patient with factor V Leiden %%%mutation%%, lupus anticoagulant, and activated protein C %%%resistance%%: a case report

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ABSTRACT: Although patients undergoing cardiac surgery often present with diverse comorbidities, those with coagulation derangements are especially challenging. The present report describes the management of a patient who presented with a Factor V Leiden %%%mutation%%, lupus anticoagulant, and acquired activated protein C %%%resistance%%. A 42-year-old female presented with acute shortness of breath and chest pain. She was otherwise healthy 1 month prior to admission when she presented with dysfunctional uterine bleeding, resulting in the transfusion of three units of packed red blood cells. Coagulation evaluation revealed that the patient had lupus anticoagulant, factor V Leiden %%%mutation%% and an activated protein C %%%resistance%%. The patient presented with an acute myocardial infarction and was found to have 90% stenosis of her left main coronary artery, moderate mitral and tricuspid regurgitation, and a left ventricular ejection fraction of 25%. An emergent off-pump coronary artery bypass procedure with placement of a vein graft to the left anterior descending artery was completed. Intraoperative thrombophilia was encountered as evidenced by both an elevated thromboelastograph(TM) coagulation index (+3.6) and an acquired %%%antithrombin%%-%%III%% deficiency. Postoperatively, the patient was placed on low molecular weight heparin, but developed heparin-induced thrombocytopenia and was switched to a direct thrombin inhibitor, argatroban. The following case report describes the coagulation management of this patient from the time of admission to discharge 43 days later, and the unique challenges this combination of hemostatic defects present to the clinicians.

11/7/17

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18355751 BIOSIS NO.: 200510050251

Chagasic cardiomyopathy is independently associated with ischemic stroke in Chagas disease

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LANGUAGE: English

ABSTRACT: Background and Purpose - Chagasic cardiomyopathy is independently associated with ischemic stroke in Chagas disease. American trypanosomiasis, Chagas disease (CD), is a major public health problem in South America. We sought to evaluate prevalence of vascular risk factors for stroke in patients with stroke caused by CD. Methods - Ninety-four consecutive CD stroke patients and 150 consecutive nonchagasic stroke patients were studied. CD was confirmed when both immunofluorescence and hemagglutination serology were positive. Data collected included age, sex, vascular risk factors, diagnostic stroke subtype (TOAST classification), and echocardiography findings. Fasting plasma levels of protein C, protein S, antithrombin, homocysteine, activated protein C resistance, IgG anticardiolipin antibodies, lupus anticoagulant, and genetic tests for the factor V Leiden and the C677T methylene tetrahydrofolate reductase gene mutation were determined. Results - CD patients had a mean age of 56.31 years compared with 61.59 years for non-CD stroke patients (P = 0.0002). Cardioembolism occurred in 56.38% of CD stroke patients compared with 9.33% in controls (P = 0.000), whereas atherothrombotic strokes occurred in 8.51% of CD strokes versus 20% in controls (P = 0.016), and small-vessel stroke in 9.57% of CD stroke patients versus 34.67% in controls (P = 0.000). Apical aneurysm (37.23% versus 0.67%; OR, 88.39), left ventricular dilatation (23.4% versus 5.33%; OR, 5.42), mural thrombus (11.7 versus 2%; OR, 6.49) and abnormal electrocardiography (ECG) (66% versus 23.33%; OR, 2.87) were significantly higher in the group of chagasic stroke patients. No statistical differences were observed in thrombophilia between both groups. The significant variables that predicted CD stroke patients on a stepwise logistical regression model were apical aneurysm, cardiac insufficiency, ECG arrhythmia, female gender, and hypertension. Conclusions - Chagasic cardiomyopathy is independently associated with ischemic stroke, whereas hypercoagulable states do not appear to be major contributors to the excess stroke risk seen in patients with CD.

11/7/18

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18294336 BIOSIS NO.: 200500211401

Thrombophilia and first arterial ischaemic stroke: a systematic review

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LANGUAGE: English

ABSTRACT: Aims: To undertake a systematic review of the literature reporting the prevalence of thrombophilia in children with a first arterial ischaemic stroke (AIS). Methods: Systematic review of case-control studies reporting data for prevalence of protein C, S, and antithrombin (AT) deficiencies, activated protein C resistance (APCr), total plasma homocysteine >95th centile, the thrombophilic mutations factor V1691 GA, prothrombin 20210GA, and MTHFR C677T in children with first, radiologically confirmed, AIS. Results: Of 1437 potentially relevant citations, 18 met inclusion criteria. A total of 3235 patients and 9019 controls had been studied. Results of meta-analyses were expressed as pooled odds ratios (OR) relating the prevalence of the thrombophilic condition in children with AIS to that in controls. The pooled OR (and 95% CI) were: protein C deficiency, 6.49 (2.96 to 14.27); protein S deficiency, 1.14 (0.34 to 3.80); AT deficiency, 1.02 (0.28 to 3.67); APCr, 1.34 (0.16 to 11.52); FV1691 GA, 1.22 (0.80 to 1.87); PT20210GA, 1.10 (0.51 to 2.34); MTHFR C677T, 1.70 (1.23 to 2.34); and total plasma homocysteine >95th centile, 1.36 (0.53 to 3.51). There was no statistical heterogeneity within these data. Conclusions: All factors examined were more common in children with first AIS than in controls, and significantly so for protein C deficiency and the MTHFR C677T mutation. The implications of thrombophilia for prognosis and recurrence need to be established before clinical recommendations can be made regarding investigation and treatment of children with AIS.

11/7/19

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18289884 BIOSIS NO.: 200500196949

High prevalence of thrombophilia among young patients with myocardial infarction and few conventional risk factors

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RECORD TYPE: Abstract  
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ABSTRACT: Background: Thrombophilia refers to series of acquired and inherited conditions that confer a tendency to thrombus formation. The exact relationship between thrombophilia and MI is not well established. Objectives: To determine the prevalence of thrombophilia, in young patients with their first MI and few conventional risk factors. Methods: We evaluated the baseline characteristics and the thrombophilia profile, including anti-cardiolipin antibodies, activated protein C resistance (APCR) with the factor V Leiden mutation, prothrombin G20210A mutation, protein C, protein S, and antithrombin-III levels, among 85 consecutive patients (<50 year old) who were admitted to CCU with their first MI. Patients were divided into two groups: group A-patients with 1 or more risk factor and group B-patients with 2 or more risk factors. Results: 92% were male and 55% with anterior wall MI. Overall, the risk factor profile was: smoking in 60%, hyperlipidemia in 42%, positive family history in 29%, hypertension in 18%, diabetes mellitus in 13%, and obesity in 8%. Forty-seven percent of patients had 1 or more risk factor (n = 40, group A) and 53% had 2 or more risk factors (n = 45, group B). The prevalence of the prothrombin mutation was 15% in group A compared to 7% in group B (p = 0.12). APCR secondary to a heterozygous genotype of factor V Leiden mutation was found in 20% in group A compared to 2% in group B (p < 0.01). Anti-cardiolipin antibodies were found in 16% in group A compared to 22% in group B (p = ns). Finally, we have found that the likelihood of identifying at least one thrombophilia marker was 50% in group A compared to 29% in group B (p = 0.046). Conclusions: The likelihood to detect at least one thrombophilia marker in young patients with MI and few conventional risk factors is significantly high. Thrombophilia may contribute to the development of MI in this specific group of young patients. Copyright 2004 Elsevier Ireland Ltd. All rights reserved.

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18281957 BIOSIS NO.: 200500189022  
Thrombophilias in patients suffering ischemic stroke. Indication and calculation of costs for evidence-based diagnostics and treatment  
ORIGINAL LANGUAGE TITLE: Thrombophilien bei Patienten mit ischaemischen Schlaganfall - Indikation und Kostenermittlung einer evidenzbasierten Diagnostik und Therapie  
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JOURNAL: Nervenarzt 76 (2): p193-201 February 2005 2005  
MEDIUM: print  
ISSN: 0028-2804 (ISSN print)  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: German

ABSTRACT: Patients with ischemic stroke are sometimes found to have an

underlying inherited (deficiency of protein C, protein S, antithrombin III, activated protein C resistance, prothrombin gene mutation, hyperhomocysteinemia) or acquired thrombophilia (lupus anticoagulant and anticardiolipin antibodies, hyperhomocysteinemia). Patient selection for thrombophilia screening is, therefore, a frequent question in managing patients with ischemic stroke. In this review we discuss patient selection and timing for laboratory tests for thrombophilia screening in stroke patients based on a literature review and we calculated overall costs per year in Germany for testing patients older than 18 years with an ischemic stroke of undetermined cause. As there is a lack of studies comparing anticoagulation with antiplatelet therapy in patients with diagnosed thrombophilia, laboratory screening for thrombophilia even in a selected group of patients with cryptogenic ischemic stroke remains of questionable value at present. An exception appears to be testing for lupus anticoagulant and anticardiolipin antibodies in younger patients with suspected antiphospholipid syndrome (two positive test results necessary), because anticoagulation seems to be superior to aspirin in patients with antiphospholipid syndrome.

11/7/21

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18202421 BIOSIS NO.: 200500109486

Effects of anticoagulation protein defect in maternal plasma on spontaneous abortion

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JOURNAL: Chinese Medical Sciences Journal 19 (4): p290-292 December 2004 2004

MEDIUM: print

ISSN: 1001-9294

DOCUMENT TYPE: Article

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LANGUAGE: English

ABSTRACT: Objective To investigate the mechanism of anticoagulation protein defect in the pathogenesis of unexplained recurrent miscarriage. Methods Fifty-seven patients with a history of unexplained abortion were enrolled as the investigation group for tests of protein C, protein S, antithrombin resistance (AT-III), as well as activated protein C resistance (APC-R). The control group consisted of fifty healthy women with a history of normal pregnancy and delivery. Blood samples were obtained for measuring serum activity of protein C, protein S, AT-III, and APC-R. Patients with positive APC-R were tested for factor V (FV) Leiden gene mutation by PCR-RFLP method. Results Of the 57 patients, 12 (21.1%), 1 (1.8%), and 5 (8.8%) cases were found with protein S, protein C, and AT-III deficiency respectively, and 13 (22.8%) cases with positive results of APC-R. Of the control group, no protein C or AT-III deficiency was ever found, whereas 2 (4.0%) volunteers were presented with protein S deficiency and 3 (6.0%) with positive results of APC-R. No FV Leiden gene mutation was identified in all the patients with positive APC-R results. Late spontaneous abortion cases had



higher incidence of anticoagulation protein defect than the early cases. Conclusion Anticoagulation protein defect may play a role in the pathogenesis of fetal loss, especially for those occurring in late stage of pregnancy.

11/7/22

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18184010 BIOSIS NO.: 200500091075

Primary thrombophilia in Mexico. V. A comprehensive prospective study indicates that most cases are multifactorial

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JOURNAL: American Journal of Hematology 78 (1): p21-26 January 2005 2005

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LANGUAGE: English

ABSTRACT: Over a 36-month period, 46 consecutive Mexican mestizos with a clinical marker associated with a primary hypercoagulable state were prospectively assessed by searching for the sticky platelet syndrome (SPS), the activated protein C %resistance% (aPCR) phenotype, coagulation protein C activity and antigen, coagulation protein S, %antithrombin% %III%, plasminogen, tissue-type plasminogen activator activity, plasminogen activator inhibitor activity, plasminogen activator inhibitor type 1, IgG and IgM isotypes of antiphospholipid antibodies, homocysteine levels, the factor V gene Leiden, Cambridge, Hong Kong, and Liverpool %mutations%, the 677 C fwdarw T %mutation% in the 5,10-methylenetetrahydrofolatereductase (MTHFR), and the G20210A polymorphism in the X-untranslated region of the prothrombin gene. Of the 46 consecutive patients prospectively accrued in the study, only 12 (26%) were males, the median age being 38 years (range 10-63 years). In only four individuals (8%) could we not record any abnormality. In 5/42 patients with abnormal results (12%), a single abnormality was recorded, whereas in the remaining 37, two to five co-existing abnormalities were identified. We found 22 (48%) patients with the SPS, 11 (24%) with the aPCR phenotype, 5 (11%) with the factor V Leiden %mutation%, 7 (15%) with the prothrombin gene %mutation%, 29 (63%) with the MTHFR gene %mutation%, 11 (24%) with the factor V HR2 haplotype, 11 (24%) with antiphospholipid antibodies, 4 (9%) with PS deficiency, 6 (13%) with PC deficiency, one with the FV Hong Kong %mutation%, and one with AT-III deficiency. The results are consonant with the idea that most cases of thrombophilia in Mexico are multifactorial. Copyright 2004 Wiley-Liss, Inc.

11/7/23

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18132183 BIOSIS NO.: 200500039248

Prevalence of factor V Leiden mutation and other hereditary thrombophilic factors in Egyptian children with portal vein thrombosis: results of a single-center case-control study

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ISSN: 0939-5555

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: No identifiable cause can be found in more than half of the cases of portal vein thrombosis (PVT). Our aim was to assess the prevalence of factor V Leiden mutation and other thrombophilic factors as risk factors in the development of PVT in the pediatric age group. From March 2001 to January 2002, 40 children with PVT were enrolled in the study, in addition to 20 age-matched and sex-matched controls. Protein C, protein S, antithrombin, and activated protein C resistance (APCR) were assayed. Molecular study of factor II and factor V mutations was carried out. Of the patients, 25 had detectable hereditary thrombophilia (62.5%), 12 had factor V Leiden mutation (30%), 11 had protein C deficiency (27.5%), 6 had factor II mutation (15%), 1 had antithrombin deficiency (2.5%), and none had protein S deficiency. Five children had concurrence of more than one defect. Factor V Leiden mutation is the most common hereditary thrombophilia associated with PVT and the relative risk of factor V Leiden mutation, as a cause of PVT, was six times more than in controls (odds ratio=6). Concurrence of more than one hereditary thrombophilic factor was seen in 12.5% of our patients. Circumstantial risk factors (neonatal sepsis, umbilical sepsis, umbilical catheterization) were not more significantly prevalent among patients with hereditary thrombophilia than among those with no detectable abnormalities in anticoagulation.

11/7/24

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18050335 BIOSIS NO.: 200400421124

Endothelial cell activation and hypercoagulability in ocular Behcets disease

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JOURNAL: American Journal of Ophthalmology 137 (5): p850-857 May 2004 2004

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LANGUAGE: English

ABSTRACT: PURPOSE: To investigate the presence of a hypercoagulable state and vascular endothelial dysfunction in patients with ocular Behcet's disease and relate the results to the activity of ocular and systemic involvement. DESIGN: Cross-sectional laboratory and clinical study. METHODS: Prospective study of blood samples of 24 patients diagnosed with ocular Behcet's disease, which were analyzed for factor VIII, factor XI, von Willebrand factor antigen and ristocetin (vWF ag and risto), ~~anti~~, ~~thrombin~~ ~~III~~ (~~ATIII~~), protein C and S, fibrinogen and activated protein C (APC) ~~resistance~~. The results were compared with 40 healthy controls and analyzed for association with ocular and systemic clinical features. RESULTS: The mean values of factor VIII, factor XI, vWF ag, vWF risto, ~~ATIII~~, and fibrinogen were significantly raised compared to healthy population (for all:  $P < .001$ ). Most striking were factor VIII activity levels above 130% in 79% (19 of 24) of our patients. 67% (16 of 24) had levels of factor VIII above 150%, which correlates with a fivefold increase in risk of thrombosis. Other prothrombogenic factors were negative in all but 2 patients (1 protein C deficiency, 1 factor V Leiden ~~mutation~~). Endothelial cell activation, measured by vWF activity, revealed elevated levels in 42% (10/24). Complete/incomplete Behcet's disease patients with present or previous macular edema had significantly higher FVIII levels than complete/incomplete Behcet's disease patients who had never shown any signs of macular edema ( $P = .04$ ). Further correlations between the laboratory results and clinical symptoms were not found. CONCLUSIONS: We found a generalized hypercoagulable state with endothelial cell activation in ocular Behcet's disease, irrespectively of current ocular disease activity.

11/7/25

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17975901 BIOSIS NO.: 200400346690

Ischemic colitis revisited: A prospective study identifying hypercoagulability as a risk factor

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JOURNAL: Southern Medical Journal 97 (2): p120-123 February 2004 2004

MEDIUM: print

ISSN: 0038-4348

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Background: Although causes for ischemic colitis have been identified, many cases are deemed idiopathic. Some reports suggest an association between ischemic colitis and coagulation disorders. Our purpose was to explore the relationship of ischemic colitis and clotting abnormalities. Methods: Eighteen patients consented to undergo a hypercoagulability evaluation. Tests included protein C, protein S, activated protein C ~~resistance~~, factor V Leiden, anticardiolipin

antibodies, antineutrophil cytoplasmic antibodies, rheumatoid factor, %antithrombin% %III%, anti-smooth muscle antibody, lupus anticoagulant panel, and prothrombin 20210G/A %mutation% (in women undergoing hormone replacement therapy). Results: Five of 18 patients tested positive for coagulation abnormalities, including factor V and activated protein C %resistance%, protein S deficiency, prothrombin 20210G/A %mutation%, and anticardiolipin antibody. Conclusion: To our knowledge, this is the largest series of patients with ischemic colitis studied for coagulation defects in the United States. The prevalence of clotting disorders in our study (28%) was higher than that in the general population (8.4%). Coagulation disorders should be considered in some cases of ischemic colitis that are thought to be idiopathic.

11/7/26

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17856169 BIOSIS NO.: 200400226224

Factor XII deficiency is strongly associated with primary recurrent abortions.

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JOURNAL: Fertility and Sterility 80 (3): p590-594 September 2003 2003

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ISSN: 0015-0282 (ISSN print)

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Objective: To evaluate factor XII deficiency in women with primary and secondary recurrent abortion. Design: Prospective case-control study. Setting: University hospital. Patient(s): Sixty-seven women with primary and 33 women with secondary recurrent abortion of unexplained nature and 49 healthy controls with no history of thrombotic disease or adverse pregnancy outcomes. Main Outcome Measure(s): Plasma factor XII activity, activated protein C %resistance%, factor V Leiden %mutation% analysis, protein C, protein S, %antithrombin% %III%, karyotyping, and anticardiolipin antibodies. Result(s): Ten of 67 women with primary recurrent abortion (14.9%) and 4 of 33 women (12.1%) with secondary recurrent abortion had reduced factor XII activity (<60%). These results are highly significant in the former group and showed a tendency toward significance in the latter group. All controls had normal factor XII activity. Conclusion(s): Factor XII deficiency is strongly associated with primary recurrent abortion, and women with secondary recurrent abortion show a tendency toward factor XII deficiency.

11/7/27

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17794467 BIOSIS NO.: 200400161808

Inherited thrombophilia in Slovak Republic.

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JOURNAL: Blood 102 (11): p114b November 16, 2003 2003

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CONFERENCE/MEETING: 45th Annual Meeting of the American Society of  
Hematology San Diego, CA, USA December 06-09, 2003; 20031206

SPONSOR: American Society of Hematology

ISSN: 0006-4971

DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Background: Several genetic risk factors for venous thrombosis (VT) were identified by studying families of thrombophilia patients (antithrombin (ATIII) deficiency, protein C (PC) and protein S (PS) deficiencies, dysfibrinogenemia, APC-resistance associated with factor V Leiden (FVL). Also the increased risk of VT was found to be associated with non-0 blood group and the prothrombin (FII) 20210A mutation in population based case-control studies. Aim of study: The main objective of our study was to determinate the most frequent genetic risk factors for VT in Slovak population. Patients and methods: 2046 patients with a history of venous thromboembolism (VTE) were examined for these genetic risk factors: 1. common - FVL (R506Q) and FII 20210A mutations, 2. less common - ATIII, PC and PS deficiencies, 3. rare - dysfibrinogenemia: and for possible risk factors of VTE - hyperhomocysteinemia, activated PC-resistance (APC-R) without presence of FVL, increased plasma levels of FVIII (FIX, FXI), FXII deficiency, heparin cofactor II (HCII) deficiency and sticky platelet syndrome. Results: The frequency of risk factors in patients with VTE was as followed: FVL-29.8%, FII 20210A - 8.6%, PS deficiency - 8.8% (including association with APC-R), PC deficiency -2.2%, ATIII deficiency - 2.1%, HC II deficiency - 0.8%, dysfibrinogenemia -0.9% and plasminogen deficiency - 0.6%. For healthy Slovak population the FVL and FII 20210A frequencies were determined 4% and 2.6%, respectively. Conclusion: We found higher FVL prevalence in Slovak population of patients with VTE (approx. 30%) compared to geographic FVL distribution in Central Europe (approx. 20%) as well as higher frequency of both PS deficiency and FII 20210A allele. The frequency of another genetic risk factors for VT in Slovakia didn't differ from those in neighbouring countries.

11/7/28

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17794440 BIOSIS NO.: 200400161781

Assessment of indications cited for thrombophilia screening in an urban health region.

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JOURNAL: Blood 102 (11): p107b November 16, 2003 2003

MEDIUM: print

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DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster  
RECORD TYPE: Abstract  
LANGUAGE: English

**ABSTRACT:** Introduction: Thrombophilia testing is an expensive diagnostic process for which there is considerable uncertainty regarding optimal patient selection for screening. Our specific objectives were to describe the indications cited for testing in an urban health region as well as to review the yield of these studies by indication. Methods: An administrative database of the thrombophilia tests performed in Southern Alberta, Canada, in 2002 was examined. The database contained demographics, indications, medical histories and test results. Exclusion criteria were subject age less than 18, health care numbers from outside the region, erroneous duplicate testing and inadequacy of information provided by the ordering physician. Testing included one or more of the following: Factor V Leiden, APC ~~Resistance~~, Factor II ~~Mutation~~, ~~Antithrombin~~ ~~III~~, Protein C, Protein S and Lupus anticoagulant. Indications for testing were categorized as first pulmonary embolism (PE); first deep vein thrombosis (DVT); recurrent PE or DVT; unusual site of venous thromboembolism (VTE); arterial thrombosis; family history of thrombosis or thrombophilia in a first degree relative; family history of thrombosis or thrombophilia in a non-first degree relative; and other. Univariate analyses were performed and frequencies calculated for the main factors. Results: Of the 906 thrombophilia studies assessed, the mean age was 43.5 and 68.3% of the subjects were female. The documented indications for testing were: a first PE (11.4%); a first DVT (15.8%); recurrent PE or DVT (12.8%); an unusual site of VTE (6.5%); arterial thrombosis (13.7%); a family history of thrombosis in a first degree or non-first degree relative (16.4% and 2.2%, respectively); a family history of thrombophilia in a first degree and non-first degree relative (7.7% and 1.3%, respectively); and other (11.8%). There was no clear indication for testing in four studies. In analysis of the test results by indication, test results were normal for 77.7% of the patients with a first PE; 71.3% of the patients with a first DVT; 70.7% of the patients with recurrent PE or DVT; 71.2% of the patients with an unusual site of VTE; 79.0% of the patients with arterial thrombosis; 68.9% of the patients with a family history of thrombosis in a first degree relative; 75.0% of the patients with a family history of thrombosis in a non-first degree relative; 44.3% of the patients with a family history of thrombophilia in a first degree relative; 75.0% of the patients with a family history of thrombophilia in a non-first degree relative; and 72.9% of patients with other reasons cited for testing. Conclusions: The most commonly cited indications for thrombophilia testing were a family history of thrombosis in a first degree relative, a first DVT, arterial thrombosis and VTE recurrence. In contrast, the yield of positive test results was highest for a less common indication - a family history of thrombophilia in a first degree relative. This combination of findings suggests that the current pattern of testing does not provide an optimal balance of effectiveness and efficiency of screening for thrombophilias, and that real-time filtering of referrals may be needed to limit testing for less appropriate indications.

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17794428 BIOSIS NO.: 200400161769

Protein S deficiency associated with right ventricular thrombosis. Followed by the appearance of a weak lupus anticoagulant.

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JOURNAL: Blood 102 (11): p104b November 16, 2003 2003

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ISSN: 0006-4971

DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract

RECORD TYPE: Abstract

LANGUAGE: English

**ABSTRACT:** Introduction: Protein S deficiency has been well established as a risk factor for venous thromboembolism. More recently, free protein S deficiency has been associated with anticardiolipin antibodies in the clinical setting of ischemic strokes. Right ventricular thrombus represents a rare complication of thrombophilias, with single cases reported in a Behcet's patient with the prothrombin gene %mutation% and in a young woman with familial heparin cofactor deficiency. Right ventricular thrombi may be an underrecognized presentation for thrombophilic patients with pulmonary embolus. We report a patient with protein S deficiency presenting with pulmonary embolus from a large right ventricular thrombus followed by the appearance of a weak lupus anticoagulant Case: A 26 year old, previously healthy African American male presented with chest pain and dyspnea. Evaluation of his symptoms included ventilation-perfusion scans interpreted as intermediate probability for the presence of a pulmonary embolus. A CTPA confirmed the presence of a right lower lobe pulmonary embolus. Lower extremity Doppler studies were negative for an acute or chronic DVT. An echocardiogram showed a mobile echodensity in the mid to distal portion of the right ventricle. Methods: A hypercoagulable workup was undertaken. This included a PT, aPTT, protein C and S, AT III, lupus anticoagulant screen, homocysteine, PCR. for prothrombin 20210A gene %mutation% and Factor V Leiden %mutation% and APC %resistance%. Results: PT and aPTT were within the normal reference range. A low functional protein S at 46% was noted. A DRVVT was noted to be borderline high at 47.6 secs. A 50:50 mix of the patient's plasma and pooled normal plasma corrected it to 41.2 seconds (normal reference range=41.5 secs). The confirmation was high at 35.7 seconds (reference range 33.5 secs) and the confirm ratio was 1.3 (reference range up to 1.3). A repeat set of labs off all anticoagulants on follow up showed a similar picture with a higher ratio of 1.5, suggesting the additional presence of a weak lupus-like anticoagulant. Management: The patient underwent a surgical procedure with thoracotomy and resection of a 2.0X2.5 cm mass under cardiopulmonary bypass. Histologic study of the resected specimen was consistent with an organizing thrombus. Cultures of the specimen were all negative. After surgery, the patient was therapeutically anticoagulated and remains well after 6 months of follow-up to date. Conclusion: To our knowledge, this represents the first reported case of a patient with functional protein S

deficiency associated with a right ventricular thrombus and pulmonary embolus. Interestingly, even though initial laboratory data did not meet the criteria for a lupus anticoagulant, a repeat study was suggestive of the presence of a weak lupus-like inhibitor.

11/7/30

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17768064 BIOSIS NO.: 200400135418

Neonatal thrombosis.

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JOURNAL: Indian Journal of Pediatrics 70 (11): p903-907 November 2003 2003

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LANGUAGE: English

ABSTRACT: Neonatal thrombosis is a serious event that can cause mortality or result in severe morbidity and disability. The most important risk factor for the development of thrombosis during the neonatal period is the presence of an indwelling central line and consequently the vessels involved tend to be those most frequently used for catheterization. Other documented risk factors for the development of neonatal thrombosis include asphyxia, septicemia, dehydration, maternal diabetes and cardiac disease. Main laboratory findings for the diagnosis of hypercoagulable states, include shortened aPTT, decreased levels of inhibitors (AT III, Protein C and Protein S), increased %resistance% to activated protein C, defective fibrinolysis (basal and after stimuli), increased levels of clotting factors (fibrinogen, factor VII, factor VIII, etc.), increased and/or hyperactive platelets, increased whole blood and/or plasma viscosity, Antiphospholipid antibodies and presence of prothrombotic molecular defects like FV Leiden, P20210 and MTHFR. Approximately 4% and 2% respectively of Caucasians are heterozygous for these gene defects. Their causative role in neonatal thrombosis is unknown but they may have a contributory role in the pathogenesis of thrombosis in neonates.

11/7/31

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17746200 BIOSIS NO.: 200400116957

Factor V Leiden (FVL) %mutation% in children with portal vein thrombosis.

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JOURNAL: Hepatology 38 (4 Suppl. 1): p415A October 2003 2003



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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Portal vein thrombosis (PVT) is a common cause of portal hypertension in children. No clear cause is identified in 50% of the cases. Factor V Leiden (FVL) mutation is characterized by poor anticoagulant response to activated protein C. However the prevalence of FVL mutation in children with PVT has not been well investigated. Due to the rarity of the condition no large studies have been done. Therefore, we studied the prevalence FVL mutation, as well as deficiencies of protein C, protein S, antithrombin (ATIII), factor II mutation and activated protein C resistance in 40 children with PVT as well as 24 healthy age and sex-matched children. Results: 25 children with PVT (62.5%) had one or more thrombophilic factor. The most common factors were FVL mutation (30%), activated protein C resistance (30%) and protein C deficiency (27.5%). None of the control group had any thrombophilic factor. Conclusion: Our results suggest that thrombophilia is common in children with PVT and Factor V Leiden (FVL) mutation is the most common disorder in these patients. To our knowledge this is the largest study that has been done in children with PVT.

11/7/32

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17665181 BIOSIS NO.: 200400035938

High prevalence of thrombophilia markers among young patients with myocardial infarction and few conventional risk factors.

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17531055 BIOSIS NO.: 200300488712

[The diagnosis of thrombophilia: Coagulologic and genetic studies.]

ORIGINAL LANGUAGE TITLE: Diagnostyka trombofilii w oparciu o badania:  
Koagulologiczne i genetyczne.  
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JOURNAL: Roczniki Pomorskiej Akademii Medycznej w Szczecinie 48 p179-193  
2002 2002  
MEDIUM: print  
ISSN: 1427-440X \_(ISSN print)  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: Polish

ABSTRACT: Venous thromboembolism and associated complications often leading to permanent disability or death are an important problem in modern medicine. Congenital or acquired disorders of the hemostatic system, such as hypercoagulation or thrombophilia, predispose to thrombosis. The aims of the study were as follows: 1. To assess the prevalence of thrombophilia in venous thromboembolism and in healthy subjects by testing **resistance** to activated protein C and other markers of hemostasis; 2. To screen for factor V Leiden with a PCR-based assay; 3. To evaluate the usefulness of the adopted analytical approach for the detection of thrombophilia in clinical practice. 29 patients (17 females and 12 males) with venous thromboembolism and a history of thrombotic episodes before the age of 40, either idiopathic or associated with protracted immobilization, pregnancy or puerperium, were enrolled in the study. The control group consisted of 25 age-matched healthy subjects (14 females and 11 males) without any history of thrombosis. The following hemostatic parameters were measured: 1. Activated protein C **resistance** (APC-R); 2. Protein C (PC) and **antithrombin** **III** (AT III) activities; 3. Protein S (PS) activity; 4. Fibrinogen (FB) concentration; 5. Euglobin lysis time (ELT); 6. Prothrombin time (PT); 7. Activated partial thromboplastin time (APTT). The presence of Leiden **mutation** was detected by PCR amplification and digestion of products with Mnl I restrictase. The results were tested statistically using: 1. Kolmogorov-Smirnov D test; 2. Student's t-test; 3. linear regression analysis; 4. chi2 test. The following conclusions were drawn: 1. Prevalence of thrombophilia in patients with venous thromboembolism is 31%, a figure consistent with literature data (no signs of thrombophilia were found in the control group); 2. **Resistance** to activated protein C is sufficient proof of Leiden **mutation** provided that APCR index (r) is less than 0.9 (borderline r values (0.9-1.1) require further genetic testing). 3. Methods of diagnosis of thrombophilia used in this study could be applied in routine clinical practice, the most useful ones being **resistance** to activated protein C, fibrinogen concentration and protein S activity. With this approach the detection of higher risk of thrombotic-embolic episodes, either acquired or inborn, is possible in most cases.

11/7/34

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17235999 BIOSIS NO.: 200300194718  
Prothrombin G20210A **mutation** and oral contraceptive use increase

upper-extremity deep vein thrombotic risk.  
AUTHOR: Vaya Amparo (Reprint); Mira Yolanda; Mateo Jose; Falco Cristina;  
Villa Piedad; Estelles Amparo; Corella Dolores; Fontcuberta Jordi; Aznar  
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JOURNAL: Thrombosis and Haemostasis 89 (3): p452-457 March 2003 2003  
MEDIUM: print  
ISSN: 0340-6245  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: The role played by a hypercoagulable state, either inherited or acquired, in the pathogenesis of upper-extremity deep vein thrombosis (UEDVT) remains a question of debate. We performed a case-control study including 79 patients with a first objectively confirmed episode of UEDVT, 31 secondary and 48 primary, and 165 healthy controls. Nine patients (11.4%) with UEDVT were carriers of the prothrombin G20210A %%%mutation%%% vs. six (3.7%) in controls;  $P=0.025$ , OR: 3.39 (95% CI 1.16 to 9.88). No statistical difference was observed between cases and controls for the factor V Leiden %%%mutation%%%, AT, protein C or protein S deficiency and anticardiolipin antibodies (ACAs). Thirteen (35.1%) UEDVT patients were oral contraceptive (OC) users vs. 12 (16%) controls;  $P=0.020$ , OR: 2.89 (95% CI 1.16-7.21). When secondary UEDVT patients were compared with controls, no differences were observed in any of the risk factors analysed. On the other hand, when primary UEDVT was considered, six (12.5%) patients were carriers of the prothrombin G20210A %%%mutation%%% vs. six (3.7%) controls;  $P=0.031$ , OR: 3.76 (95% CI 1.15-12.26). Regarding ACAs, a borderline statistical significance was observed when primary UEDVT was compared with controls,  $P=0.048$ ; OR: 4.88 (95% CI 1.05-22.61). In primary UEDVT, 52% of the fertile women were OC users vs. 16% of controls;  $P=0.001$ , OR: 5.78 (95% CI 2.13-15.67). When the interaction of both factors, i.e. prothrombin G20210A %%%mutation%%% and OC intake, were considered, the risk increased markedly, indicating a synergistic effect as observed with other thrombotic locations. In patients with primary UEDVT screening for antithrombin, protein C and protein S deficiency and APC %%%resistance%%% would not be justified, although it might be reasonable to determine the carrier status of the prothrombin G20210A %%%mutation%%% only in OC users.

11/7/35  
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17235704 BIOSIS NO.: 200300194423  
Incidence of thrombophilia detected in southern Taiwanese patients with  
venous thrombosis.  
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JOURNAL: Annals of Hematology 82 (2): p114-117 February 2003 2003

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LANGUAGE: English

ABSTRACT: In order to analyze the incidence of thrombophilia in southern Taiwan, we studied the prevalence of antithrombin (AT), protein C (PC), and protein S (PS) deficiencies, the prevalence of factor V Leiden mutation, and the presence of acquired lupus anticoagulant (LA) and anticardiolipin antibody (ACA) in 56 patients 65 years old with deep venous thrombosis (DVT). Of 56 patients, 30 were male, 26 female, and the mean age of the patients was 43 years (18-65 years). None had factor V mutation or activated PC resistance; 21 patients (37.5%) showed abnormal results: 4 (7.1%) had AT deficiencies, 6 (10.7%) PC deficiencies, 6 (10.7%) PS deficiencies, 2 (3.6%) a combined PC and PS deficiency, and 3 (5.4%) LA and ACA. Only PC and PS deficiencies were significantly associated with increased risk for the development of thrombosis with an odds ratio of 4.2 (95% confidence interval: 1.2-15.0, P=0.018) and 8.1 (95% confidence interval: 1.6-40.6, P=0.003), respectively. We concluded that the prevalence of heritable thrombophilia (34.0%) in Taiwan is higher than that in Western countries, but that it is lower than previously reported in Hong Kong and Taiwan. We attribute this to selection bias.

11/7/36

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17215184 BIOSIS NO.: 200300173903

Activated protein C resistance in normal and pre-eclamptic pregnancies.

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JOURNAL: Gynecologic and Obstetric Investigation 54 (3): p145-149 2002  
2002

MEDIUM: print  
ISSN: 0378-7346  
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RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Objectives: A lower ratio in the classic activated protein C resistance (APC-R) test has been reported during pregnancy, which has been called 'acquired' APC-R. However, little is known about the cause of the lowered ratio, and whether or not there is a correlation with blood coagulation activation. The primary objective of our study was to determine changes in APC-R levels in each of the trimesters of normal pregnancy. The secondary objective was to confirm whether APC-R levels were lower in pregnancies complicated by pre-eclampsia than in a control group. Finally, this prospective study was performed to investigate the prevalence of APC-R among pregnant women and to elucidate its obstetric consequences. Methods: We enrolled 35 healthy pregnant women and 47

pregnant women affected by pre-eclampsia in our study. The following laboratory tests were performed: prothrombin time, partial thromboplastin time, fibrinogen levels, antithrombin, plasminogen activator, plasminogen activator inhibitor-1 (as a marker of endothelial damage), haptoglobin (as a marker of intravascular haemolysis), a functional test for APC-R and analysis of factor V Leiden mutation by polymerase chain reaction. Results: The activated protein C sensitivity ratio was lower in the pathological group than in the control group ( $p=0.008$  and  $p=0.02$ , respectively). Plasminogen activator was found to be higher in the pathological group than in the control group ( $p=0.05$ ). Finally, the overall prevalence of factor V Leiden mutation was 5.4%, i.e. 2/35 women (5.7%) in the control group and 3/47 women in the pathological group (6.38%). Conclusions: The APC ratio decreased after 20 weeks of gestation until week 42. This decrease was most pronounced in the third trimester, in which resistance was demonstrated in 34.2% of control group patients. In pre-eclampsia, we found a greater reduction of the APC ratio than in controls. We hypothesise that this is due to a decrease in the plasminogen levels of coagulation inhibitors and an increase in coagulatory factors.

11/7/37

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16712381 BIOSIS NO.: 200200305892

Combination of heterozygote factor V Leiden carriage with erythrocytosis as a cause of deep vein thrombosis of the leg

AUTHOR: Idelson L I; Albert I I; Rudensky B R; Levy-Lahad E; Renbaum P; Klein G

JOURNAL: Terapevticheskii Arkhiv 74 (2): p66-70 2002 2002

MEDIUM: print

ISSN: 0040-3660

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: Russian

ABSTRACT: Aim: To reject one of the variants of inherited thrombophilia in a 64-year-old patient with deep thrombosis of leg veins and high hemoglobin and red cell levels. Material and methods: The study was made of antithrombin, plasminogen activator, plasminogen activator inhibitor-1 to activated protein C; molecular structure of DNA coding factor 5; methylenetetrahydrofolate reductase. Results: The patient was diagnosed to have heterozygote factor V Leiden mutation. The replacement of arginin by glutamin in position 506 of factor V molecule raises the risk of thrombosis. This risk was aggravated by high hemoglobin, red cells, hematocrit, low volume of circulating plasm, smoking. The patient had normal levels of leukocytes and platelets, normal spleen size, slightly lowered level of erythropoietin. Conclusion: The presence of thrombosis in patients with erythremia or erythrocytosis rejects one of the thrombophilia forms.

11/7/38

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16620595 BIOSIS NO.: 200200214106

Thrombophilia is common in women with idiopathic pregnancy loss and is associated with late pregnancy wastage  
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JOURNAL: Fertility and Sterility 77 (2): p342-347 February, 2002 2002  
MEDIUM: print  
ISSN: 0015-0282  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Objective: To describe the characteristics of thrombophilia in women with idiopathic pregnancy loss. Design: Prospective observational study. Setting: Tertiary referral center in a teaching academic hospital. Patient(s): One hundred forty-five patients with repeated pregnancy loss and 145 matched controls. Intervention(s): Prospective assessment of thrombophilia in patients and controls. Main Outcome Measure(s): Prevalence of activated protein C (APC) resistance, protein C, protein S, and antithrombin deficiencies, antiphospholipid antibodies, factor V Leiden, factor II G20210A, and MTHFR C677T mutations. Result(s): At least one thrombophilic defect was found in 66% of study group patients compared with 28% in control group patients. Combined thrombophilic defects were documented in 21% of women with pregnancy loss compared with 5.5% of control patients. Late pregnancy wastage occurred more frequently in women with thrombophilia compared with women without thrombophilia (160/429 (37%) vs. 39/162 (24%), respectively). APC resistance was documented in 39% of women with pregnancy loss compared with 3% of the control patients. APC resistance without factor V Leiden mutation was documented in 18% of women with pregnancy loss compared with none of the controls. While factor V Leiden mutation was more common in women with pregnancy loss (25% vs. 7.6%), factor II G20210A and homozygosity for MTHFR C677T contributed to pregnancy loss only in the presence of other thrombophilia. Conclusion(s): Thrombophilia was found in the majority (66%) of women with idiopathic pregnancy loss. APC resistance with or without factor V Leiden mutation is the most common thrombophilic defect, and combined thrombophilia is a frequent finding in women with pregnancy loss. Thrombophilia is associated with increased frequency of late pregnancy wastage.

11/7/39  
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16617567 BIOSIS NO.: 200200211078  
Role of acquired and hereditary thrombotic risk factors in patients with ischemic colitis  
AUTHOR: Koutroubakis Ioannis E (Reprint); Sfiridaki Aekarinerini; Theodoropoulou Angeliki; Livadiotaki Aekaterini; Dimoulios Philippos; Kouroumalis Elias A  
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JOURNAL: Gastroenterology 120 (5 Supplement 1): pA.282 April, 2001 2001  
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CONFERENCE/MEETING: 102nd Annual Meeting of the American

Gastroenterological Association and Digestive Disease Week Atlanta,  
Georgia, USA May 20-23, 2001; 20010520

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American Association for the Study of Liver Diseases  
American Society for Gastrointestinal Endoscopy  
Society for Surgery of the Alimentary Tract

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11/7/40

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16614087 BIOSIS NO.: 200200207598

[Inherited thrombophilia in the Great Poland region.]

ORIGINAL LANGUAGE TITLE: Wrodzona trombofilia w regionie wielkopolskim

AUTHOR: Lewandowski Krzysztof (Reprint); Kwasnikowski Piotr; Rozek Marek;  
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JOURNAL: Acta Haematologica Polonica 32 (3): p295-303 2001 2001

MEDIUM: print

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LANGUAGE: Polish

ABSTRACT: In the past a lot of studies of molecular basis of thrombophilia focused on the identification of a deficiency state. Moreover, a recognised defect i.e. protein S (PS), protein C (PC) or antithrombin (AT) deficiency were reported to be associated with an increased risk of venous thromboembolic disease (VTED). In recent years this situation has changed considerably because of the identification of patients with combined prothrombotic abnormalities. The aims of the study were: 1) investigation of the prevalence of prothrombotic defect in patients from the Great Poland region with at least one episode of VTED 2) evaluation of the frequency of combined thrombophilic abnormalities in this group of persons. Study groups consisted of consecutive patients aged 14-68 years with the objective diagnosis of an episode of VTED, who were investigated between January 1995 to December 2000 in the Department of Haematology Academy of Medical Sciences in Poznan, Poland. The control group consisted of healthy volunteers. AT deficiency was confirmed in 6.5% of patients. Decreased PC activity was found in 7% of investigated persons. Reduced free PS level in the plasma was detected in 6% of patients. Abnormal result of APC-%%resistance%% test was confirmed in 13.8% of persons suffering from VTED. The results of genetic examination revealed the presence of FVLeiden in 19.1% (homozygotes 0.9%), prothrombin G20210A in 8.6% (homozygotes 0.5%), factor V A4070G in 14.7% (homozygotes 0.7%), C677T abnormality of MTHFR gene in 44.8% (homozygotes 6.9%) of cases. The presence of combined prothrombotic defects was confirmed in about 20% of FVLeiden symptomatic carriers (in 13.1% patients in combination with C677T %%mutation%% of MTHFR gene and in 5.3% of patients with prothrombin G20210A allele presence). In the healthy controls the

frequency of FVLeiden was 4.1% (heterozygotes), FV A4070G 10.9% (heterozygotes), polymorphism G20210A of prothrombin gene 0.8% (heterozygotes) and C677T mutation of MTHFR gene in 54.6% (heterozygotes 43%, homozygotes 11.6%). Between investigated patients with VTED and healthy controls the FV Arg306fwdarwThr and FV Arg306fwdarwGly mutations of the FV gene were not found. Our results confirm high frequency of combined prothrombotic defects in VTED patients from Great Poland. This phenomenon could lead to the overestimation of the role of single deficiency in the pathogenesis of venous thrombosis.

11/7/41

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16603233 BIOSIS NO.: 200200196744

Hereditary thrombophilia in elite athletes

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JOURNAL: Medicine and Science in Sports and Exercise 34 (2): p218-221

February, 2002 2002

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Purpose: Although under normal circumstances exercise prevents thrombosis, there are cases in the literature that indicate a connection between exercise and the onset of thrombosis. In the average population, hereditary thrombophilia is a major cause of thrombosis. However, nothing is known about the prevalence of hereditary thrombophilia in elite athletes. Because high-performance sports are known to carry an increased risk of thrombogenesis, measures to avoid thrombosis must be initiated in cases of known hereditary thrombophilia. Methods: Hereditary thrombophilia was checked for in 173 elite athletes, members of the German national team. Antithrombin, protein C, protein S, and the APC ratio, followed by a molecular genetic analysis, were measured, and molecular analysis of factor II G20210A mutation was used to detect the presence of an antithrombin, protein C-and protein S-deficiency, as well as factor V Leiden (factor V 506Arg to Gln) and factor II G20210A mutation. Results: No definite antithrombin, protein C- or protein S-deficiency was found. In 12 cases, an APC resistance caused by a factor V Leiden mutation (11 heterozygous; 1 homozygous) was detected. In 10 cases, a heterozygous factor II G20210A was observed; a combination of both mutations was not found. For factor V Leiden, this corresponds to a prevalence of 6.9% (CI 95% 3.6-11.8%) in our group, similar to prevalence rates in the general population. Additionally, the observed prevalence of 5.8% (CI 95% 2.8-10.4%) of factor II G20210A is nearly within the range as reported by several authors. Conclusion: Based on the observed prevalence of APC resistance and factor II G20210A mutation in our group of athletes, along with consideration of additional circumstantial risks, screening tests for elite athletes should be



considered to allow the undertaking of preventive measures.

11/7/42

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16558192 BIOSIS NO.: 200200151703

Cerebral venous thrombosis and thrombophilia

AUTHOR: Grasa Jose Maria (Reprint); Montanes Maria Angeles; Sanchez-Marin Belen; Torres Manuel; Latorre Ana; Calvo Maria Teresa; Marta Javier; Rite-Gracia Segundo; Garcia Erce Jose Antonio; Giralte Manuel

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JOURNAL: Blood 98 (11 Part 2): p89b November 16, 2001 2001

MEDIUM: print

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SPONSOR: American Society of Hematology

ISSN: 0006-4971

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Background: Cerebral venous thrombosis (CVT) is a relative unusual pathology, probably underdiagnosed; nevertheless, sensitive neuroimaging techniques are increasing this diagnosis. Oral anticoagulant therapy started after diagnosis can be influenced for the existence of some hypercoagulability states. In this study the frequency of inherited thrombophilic risk factors in a population of spanish CVT patients was evaluated. Patients and methods: Hypercoagulability studies were developed for patients suffering radiologically confirmed CVT during a 3 year period (1998-2000). Patients with infectious processes close to the central nervous system were excluded. Prothrombin time, aPTT, protein C, protein S and antithrombin activity, screening and confirmatory tests for lupus anticoagulant (LA), and activated protein C resistance (APCR) were tested in an automated analyzer ACL Futuraa Plus (Instrumentation Laboratory). Genetic tests for G1691A factor V (Factor V Leiden), G20210A prothrombin and C677T methylentetrahydrofolate reductase (MTHFR) were performed by RFLP-PCR. Computer database was used for descriptive statistics. Positive LA tests were repeated three months after to confirm diagnosis of antiphospholipid syndrome. Results: 16 patients with CVT (M/F:6/10) were screened for inherited and acquired coagulation disorders. Mean age of 23.66 years with standard deviation of 19.74 years. Two older patients had antecedents of thrombosis (ischemic stroke and deep-vein thrombosis in leg). As associated clinical risk factors, two females were pregnant, one was having contraceptive therapy and one had Behcet's disease. Inherited thrombophilic risk factors were identified in 6 (37.5%) of the 16 patients studied: 1 heterozygosis factor V Leiden, 2 heterozygosis G20210A prothrombin, 2 homocystosis C677T MTHFR and 1 hereditary antithrombin activity deficiency. APCR proved to be a reliable screening method for factor V Leiden mutation. 7 LA were found, of which 6 were permanent, one associated with Factor V Leiden and other with prothrombin G20210A. Eight heterozygotes for C677T MTHFR were also found, but this is not a well-defined vascular risk factor. Comments: Although this is a small series, we found a high incidence of hereditary (37.5%) and acquired

(37.5%) thrombophilia in patients with CVT, similar to other published series (Stolz E et al. Acta Neurol Scand 2000; 102:31-6). Our results shows screening for inherited thrombophilia should be an integral part in the diagnostic process of CVT patients. Patients with inherited and acquired hypercoagulability should follow recommendations for a longer period of oral anticoagulation.

11/7/43

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16289350 BIOSIS NO.: 200100461189

Thrombophilic factors in chronic thromboembolic pulmonary hypertension

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JOURNAL: Blood Coagulation and Fibrinolysis 12 (6): p427-432 September, 2001 2001

MEDIUM: print

ISSN: 0957-5235

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LANGUAGE: English

ABSTRACT: Chronic thromboembolic pulmonary hypertension (CTE-PH) is an infrequent cause of pulmonary hypertension that develops in 0.1-0.2% of patients who survive after an acute venous thromboembolic event. According to the largest series so far reported, 15-30% of patients with diagnosis of CTE-PH have an underlying congenital or acquired hypercoagulable state. To determine the prevalence of thrombophilic factors in our population, we analyzed 24 patients admitted to our institution between November 1992 and March 2000 fulfilling criteria for CTE-PH. Eighteen patients disclosed abnormal results in the screening for thrombophilia. The presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies) was the abnormality most frequently found (12 out of 24 patients). We found hyperhomocysteinaemia in 7/14, true protein S deficiency in 1/10, protein C deficiency in 1/13, activated protein C %resistance% in 1/22, %antithrombin% %III% deficiency in 1/24, and prothrombin gene G20210A %mutation% in 1/18 patients. Factor V Leiden was normal in all 18 patients studied. Five patients (20.8%) disclosed more than one thrombophilic abnormality. In conclusion, contrary to the largest series of patients with CTE-PH so far reported, we found that 75% of patients with CTE-PH presented at least one thrombophilic risk factor, being antiphospholipid antibodies in 50% of the cases. We recommend a thorough screening for thrombophilia in all patients with diagnosis of CTE-PH.

11/7/44

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16165673 BIOSIS NO.: 200100337512

Thrombophilia and adverse pregnancy outcome

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JOURNAL: Croatian Medical Journal 42 (2): p135-145 April, 2001 2001  
MEDIUM: print  
ISSN: 0353-9504  
DOCUMENT TYPE: Article; Literature Review  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Congenital and acquired thrombophilias are the most common predisposing factors for thromboembolism, but they may also contribute to pathophysiological processes involved in recurrent pregnancy loss, fetal death, intrauterine growth restriction, placental abruption, placental infarction, and pre-eclampsia. The most common thrombophilias are deficiencies of antithrombin, protein C, and protein S, acquired protein C resistance, genetic mutation encoding for factor V Leiden, prothrombin gene, and inherited hyperhomocysteinemia, and antiphospholipid syndrome. Although adverse pregnancy outcomes are more common in women with thrombophilia, the current evidence does not support routine thrombophilia screening of all pregnant women. Selective thrombophilia screening may be justified in certain group of women, particularly those with a history of thromboembolism. More research is required to confirm or refute the causal link between thrombophilia and abnormal placentation, and assess effectiveness and safety of thromboprophylaxis in pregnant women.

11/7/45

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16156236 BIOSIS NO.: 200100328075

Postnatal screening for thrombophilia in women with severe pregnancy complications

AUTHOR: Alfirevic Zarko (Reprint); Mousa Hatem A; Martlew Vanessa; Briscoe Lesley; Perez-Casal Marga; Toh Cheng Hock  
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UK\*\*UK

JOURNAL: Obstetrics and Gynecology 97 (5 Part 1): p753-759 May, 2001 2001  
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ISSN: 0029-7844  
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RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Objective: To examine the prevalence of maternal thrombophilia in women with severe preeclampsia/eclampsia, placental abruption, fetal growth restriction, and unexplained stillbirth. Methods: We studied 102 women who had pregnancy complications and 44 healthy women with uncomplicated pregnancies. All women were tested 10 weeks postpartum for mutations of factor V Leiden, methylenetetrahydrofolate reductase (MTHFR) C677T, and G20210A prothrombin gene; deficiencies of protein C, protein S, and antithrombin; and the presence of lupus anticoagulant and anticardiolipin antibodies. We aimed to recruit 100 cases and 300 controls to detect a 10% difference in thrombophilia

between the groups. However, we were able to recruit only 44 controls. Results: Abnormal thrombophilia screen was found in 54 women with pregnancy complications (53%) and in 17 women (39%) with normal pregnancies (odds ratio (OR) 1.8; 95% confidence interval (CI) 0.87, 3.67). %Mutations% encoding for factor V Leiden, G20210A prothrombin gene, and MTHFR C677T (homozygous) were identified in 18% of women with complications compared with 16% of controls (OR 1.1; 95% CI 0.44, 2.94). Activated protein C %resistance%, not due to factor V Leiden %mutation%, was the most common thrombophilic defect, found in 26% of women with pregnancy complications compared with 18% of controls (OR 1.5; 95% CI 0.63, 3.73). Twenty women with complications (20%) had multiple thrombophilic defects compared with four controls (9%) (OR 2.4; 95% CI 0.78, 7.61). Conclusion: In our cohort of women with pregnancy complications, maternal thrombophilia was less common than previously thought, and multiple thrombophilias were not a major additional risk factor.

11/7/46

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16132820 BIOSIS NO.: 200100304659

Utilization of testing for common inherited thrombotic disorders in a reference laboratory

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JOURNAL: Blood 96 (11 Part 2): p88b November 16, 2000 2000

MEDIUM: print

CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of

Hematology San Francisco, California, USA December 01-05, 2000; 20001201

SPONSOR: American Society of Hematology

ISSN: 0006-4971

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: BACKGROUND/OBJECTIVE: Deep-vein thrombosis is a common complication of several inherited and acquired disorders. It is, therefore, important to be able to identify inherited thrombotic disorders in order to successfully prevent possible recurrent venous thrombosis and/or pulmonary embolism in potentially affected family members. Although functional assays are recommended for initial screening for many inherited thrombotic disorders, our reference laboratory offers both functional and nonfunctional tests for several of the more common inherited thrombotic disorders (factor V Leiden (FVL) and protein C, protein S and %antithrombin% %III% (%ATIII%) deficiencies), and a PCR-based assay for detection of the prothrombin G20210A %mutation%. We were interested to determine whether appropriate tests were being requested in order to accurately and efficiently diagnose these five disorders and/or whether the number of orders for each test was consistent with their relative prevalence. METHODOLOGY: We prospectively evaluated laboratory test ordering patterns at ARUP for five common inherited thrombotic disorders (FVL, prothrombin G20210A %mutation%, and protein C, protein S, and %ATIII% deficiencies) for up to 20 months from November 1998 through June 2000. RESULTS: The

ATIII enzymatic test, a functional assay, was ordered an average of 2.5 times more frequently per month than the ATIII antigen test, while antigenic tests for protein C and protein S were ordered approximately 1.8 and 1.7 times more frequently, respectively, than protein C and protein S functional assays. The FVL PCR test was ordered 3.8 times more frequently per month than the APC resistance assay, a functional assay for the detection of FVL. The number of orders for prothrombin mutation tests was 2.8 times less per month than the ATIII functional assay, even though this mutation is approximately five times more prevalent than ATIII deficiency.

CONCLUSIONS: Although functional assays are recommended for screening for protein C, protein S, and ATIII deficiencies, and for detection of FVL, only in the case of ATIII was a functional assay ordered more frequently than a nonfunctional test. In addition, the number of ATIII tests ordered was much greater, and the number of prothrombin mutation tests much less, than warranted by the relative prevalence of each of these disorders. Hematologists and clinical pathologists are in a unique position to guide clinicians in appropriate test ordering for inherited thrombotic disorder identification.

11/7/47

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15972403 BIOSIS NO.: 200100144242

Associated prothrombotic abnormalities in patients with inflammatory bowel disease

AUTHOR: Magro F (Reprint); Dinis-Ribeiro M (Reprint); Araujo F; Correia M (Reprint); Fraga M; Cunha-Ribeiro L M; Tome-Ribeiro (Reprint)

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JOURNAL: American Journal of Gastroenterology 95 (9): p2505 September, 2000 2000

MEDIUM: print

CONFERENCE/MEETING: 65th Annual Scientific Meeting of the American College of Gastroenterology New York, New York, UK October 13-18, 2000; 20001013

SPONSOR: American College of Gastroenterology

ISSN: 0002-9270

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

11/7/48

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15872029 BIOSIS NO.: 200100043868

Diagnostic testing for coagulopathies in patients with ischemic stroke

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JOURNAL: Stroke 31 (12): p3067-3078 December, 2000 2000

MEDIUM: print

ISSN: 0039-2499

DOCUMENT TYPE: Article; Literature Review

RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Background: Hypercoagulable states are a recognized, albeit uncommon, etiology of ischemic stroke. It is unclear how often the results of specialized coagulation tests affect management. Using data compiled from a systematic review of available studies, we employed quantitative methodology to assess the diagnostic yield of coagulation tests for identification of coagulopathies in ischemic stroke patients. Summary of Review: We performed a MEDLINE search to identify controlled studies published during 1966-1999 that reported the prevalence of deficiencies of protein C, protein S, antithrombin, plasminogen, activated protein C resistance (APCR)/factor V Leiden mutation (FVL), anticardiolipin antibodies (ACL), or lupus anticoagulant (LA) in patients with ischemic stroke. The cumulative prevalence rates (pretest probabilities) and positive likelihood ratios for all studies and for those including only patients aged  $\leq 50$  years were used to calculate posttest probabilities for each coagulopathy, reflecting diagnostic yield. The cumulative pretest probabilities of coagulation defects in ischemic stroke patients are as follows: LA, 3% (8% for those aged  $\leq 50$  years); ACL, 17% (21% for those aged  $\leq 50$  years); APCR/FVL, 7% (11% for those aged  $\leq 50$  years); and prothrombin mutation, 4.5% (5.7% for those aged  $\leq 50$  years). The posttest probabilities of ACL, LA, and APCR increased with increasing pretest probability, the specificity of the tests, and features of the patients' history and clinical presentation. Conclusions: The pretest probabilities of coagulation defects in ischemic stroke patients are low. The diagnostic yield of coagulation tests may be increased by using tests with the highest specificities and by targeting patients with clinical or historical features that increase pretest probability. Consideration of these data might lead to more rational ordering of tests and an associated cost savings.

11/7/49

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15862329 BIOSIS NO.: 200100034168

Prothrombotic abnormalities in patients with Inflammatory Bowel Disease

AUTHOR: Araujo F (Reprint); Magro F; Dinis-Ribeiro M; Fraga M (Reprint);  
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JOURNAL: Haemostasis 30 (Suppl. 1): p28 May, 2000 2000

MEDIUM: print

CONFERENCE/MEETING: 16th International Congress on Thrombosis Porto,  
Portugal May 05-08, 2000; 20000505

SPONSOR: Mediterranean League Against Thromboembolic Diseases  
Portuguese Society of Thrombosis and Hemostasis

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LANGUAGE: English

11/7/50

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15858914 BIOSIS NO.: 200100030753

Life threatening thrombosis in a woman with two homozigous genetic defects related to thrombophilia

AUTHOR: Sousa S (Reprint); Araujo F; Bras C (Reprint); Esteves C (Reprint); Ribeiro P (Reprint); Ribeiro L M C; Pereira I (Reprint)

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JOURNAL: Haemostasis 30 (Suppl. 1): p104-105 May, 2000 2000

MEDIUM: print

CONFERENCE/MEETING: 16th International Congress on Thrombosis Porto, Portugal May 05-08, 2000; 20000505

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11/7/51

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15858197 BIOSIS NO.: 200100030036

Thrombophilic profile in patients with arterial or venous thrombosis

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JOURNAL: Haemostasis 30 (Suppl. 1): p104 May, 2000 2000

MEDIUM: print

CONFERENCE/MEETING: 16th International Congress on Thrombosis Porto, Portugal May 05-08, 2000; 20000505

SPONSOR: Mediterranean League Against Thromboembolic Diseases  
Portuguese Society of Thrombosis and Hemostasis

ISSN: 0301-0147

DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster

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LANGUAGE: English

11/7/52

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15834307 BIOSIS NO.: 200100006146

Do placental lesions reflect a thrombophilia state in women with adverse pregnancy outcome?

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JOURNAL: Journal of Obstetrics and Gynaecology (Abingdon) 20 (Suppl. 1): p S63 2000 2000

MEDIUM: print

CONFERENCE/MEETING: Fifth Annual Conference of the British Maternal and Fetal Medicine Society London, England, UK March 30-31, 2000; 20000330

SPONSOR: British Maternal and Fetal Medicine Society  
ISSN: 0144-3615  
DOCUMENT TYPE: Meeting; Meeting Abstract  
RECORD TYPE: Citation  
LANGUAGE: English

11/7/53

DIALOG(R)File 5:Biosis Previews(R)  
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15693135 BIOSIS NO.: 200000411448

Do placental lesions reflect thrombophilia state in women with adverse pregnancy outcome?

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JOURNAL: Human Reproduction (Oxford) 15 (8): p1830-1833 August, 2000 2000

MEDIUM: print

ISSN: 0268-1161

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: We examined the relationship between placental histology and thrombophilia status in women who were admitted with severe pre-eclampsia/eclampsia, placental abruption, intrauterine growth restriction or unexplained stillbirth. All women had thrombophilia screen at least 10 weeks after delivery (antithrombin, protein C, protein S, activated protein C resistance, anticardiolipin antibodies, lupus anticoagulant, fasting plasma homocysteine and specific mutations to methylenetetrahydrofolate reductase C677T, G20210A prothrombin gene and factor V Leiden. Placental histology reports were examined to identify the frequency of thrombotic lesions in the placenta including fetal stem vessel thrombosis, fetal thrombotic vasculopathy, placental infarction, perivillous fibrin deposition, intervillous thrombosis and placental floor infarction. During a 17 month period, a cohort of 79 women met the study criteria. Thirty (70%) out of 43 women with abnormal thrombophilia screen had abnormal placental histology. Twenty-eight (78%) out of 36 women with negative thrombophilia screen had abnormal placetae. No specific histological pattern could be identified when thrombophilia positive and thrombophilia negative groups were compared. We propose that there is a poor correlation between thrombophilia status and pathological changes of the placenta in women with severe pregnancy complications.

11/7/54

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15667668 BIOSIS NO.: 200000385981

The molecular basis of inherited thrombophilia

AUTHOR: Manucci P M (Reprint)

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JOURNAL: Vox Sanguinis 78 (Suppl. 2): p39-45 July, 2000 2000

MEDIUM: print



ISSN: 0042-9007

DOCUMENT TYPE: Article; Literature Review

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Even though it has been known for centuries that inherited defects of blood coagulation cause lifelong bleeding disorders, the existence of the counterpart, inherited thrombotic disorders, has been appreciated for only a few decades. Inherited thrombophilia can be defined as a genetically determined tendency to venous thromboembolism which characteristically occurs at a young age with no apparent cause and tends to recur. This article reviews the prevalence, biochemical and molecular basis of inherited thrombophilia, describes the main clinical manifestations and provides general guidelines for treatment. It is restricted to the more frequent and well-established causes of thrombophilia: antithrombin, protein C and protein S deficiency; resistance to activated protein C caused by mutations in coagulation factor V; and the gain-of-function mutation of factor II (prothrombin). Other causes of inherited thrombophilia are much rarer, such as dysfibrinogenemia, or not firmly established, such as abnormalities of the fibrinolytic system (plasminogen, histidin-rich glycoprotein) and thrombomodulin.

11/7/55

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15538655 BIOSIS NO.: 200000256968

Homocysteinemia (Hcy), factor V Leiden (FV1691A) and prothrombin gene mutation (PT20210A), activated protein C resistance (APCr), antithrombin deficiency (ATIIIId), protein C and protein S deficiency (PCd, PSd), lupus anticoagulant (LAC) and anticardiolipin antibodies (ACA) in patients with inflammatory bowel disease (IBD)

AUTHOR: Abbati Gianluca (Reprint); Ventura Paolo; Marietta Marco; Panini Rossana; Salvioli Gianfranco; Grandi Marco

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JOURNAL: Gastroenterology 118 (4 Suppl. 2 Part 1): pAGA A339 April, 2000  
2000

MEDIUM: print

CONFERENCE/MEETING: 101st Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Diego, California, USA May 21-24, 2000; 20000521

SPONSOR: American Gastroenterological Association

ISSN: 0016-5085

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

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11/7/56

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15439818 BIOSIS NO.: 200000158131

Screening for a prothrombotic diathesis in patients attending family planning clinics

AUTHOR: Kalev Maggie; Day Tony; Van de Water Neil; Ockelford Paul (Reprint)  
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JOURNAL: New Zealand Medical Journal 112 (1096): p358-361 Sept. 24, 1999  
1999  
MEDIUM: print  
ISSN: 0028-8446  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Aims: 1. To determine the frequency of prothrombotic markers in young women seeking a new or a repeat prescription of the oral contraceptive pill and perceived to be at high risk of thrombosis. 2. To assess cost-effectiveness of thrombophilia testing within this population. 3. To determine the frequency of acquired activated protein C (APC) resistance. Methods: Results of thrombophilia testing were retrospectively reviewed on 220 consecutively referred patients' plasmas. Women tested were clients attending local family planning clinics for a new or repeat contraceptive prescription. Samples for testing were collected by the Community Laboratory Service. Investigations included: antithrombin (AT III), protein C, protein S, APC resistance, factor V Leiden mutation analysis and anti-cardiolipin antibodies. Results: Abnormalities were detected in 35 (15.9%) of the 220 women tested. No patient had all tests performed. The most frequently detected abnormality was an increased APC resistance in 6.8% of the women tested. Three of the 13 patients with an abnormal APC resistance had a discrepancy between the low APC ratio and a negative mutation analysis result for factor V Leiden, suggesting acquired APC resistance. Deficiency of protein C was found in 1.2% (of 162), protein S in 2.0% (of 140), antithrombin (AT III) in 0.6% (of 159). Low-titre anti-cardiolipin antibodies were detected in 13.9% of this group (115 tested). Conclusions: The frequency of abnormal thrombophilia markers detected in this cohort of young women is not significantly different from that seen in a control population. This low incidence suggests that testing has been applied on a population screening basis, rather than preselecting a high-risk group. Thrombophilia screening in this patient group cannot be justified when the clinically relevant end-point is death from pulmonary embolism. The cost of preventing one fatal pulmonary embolism arising as a consequence of screening for activated protein C resistance due to the commonly occurring factor V Leiden is a minimum dollar sign25 000 000. This compares very unfavourably with the estimated cost per life saved in the National Breast Screening Programme.

11/7/57

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15398592 BIOSIS NO.: 200000116905

Causes of venous thrombosis in fifty Chinese patients

AUTHOR: Ho Chao-Hung (Reprint); Chau Wing-Keung; Hsu Hui-Chi; Gau Jyh-Pyng; Yu Tarng-Jenn

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JOURNAL: American Journal of Hematology 63 (2): p74-78 Feb., 2000 2000

MEDIUM: print  
ISSN: 0361-8609  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: In a whole year from July 1997 to June 1998, a total of 50 patients with sonogram-proved venous thrombosis who called on our hematology clinic consecutively entered into the study. Their mean age was 59.1 +/- 17.5 years, range 18-83 years, and 29 were male. A series of examinations were performed in order to find out the cause of venous thrombosis. These examinations included antithrombin, protein C, protein S, plasminogen, heparin cofactor II, activated protein C ratio, factor V Leiden %mutation%, fibrinogen, factors VIII and XII, euglobulin lysis time, 677 CfwdarwT %mutation% of methylenetetrahydrofolate reductase (MTHFR), prothrombin 20210 (PT 20210) A allele %mutation%, lupus anticoagulant, anticardiolipin antibody, and complete blood count. Five patients (10%) were found to have malignancy; an inferior vena cava thrombosis in one patient was due to venous compression by hydronephrosis; two patients had lupus anticoagulant; two had varicose veins of legs; two had protein C deficiency; four had protein S deficiency; two had plasminogen deficiency; two had antithrombin deficiency. No activated protein C %resistance%, elevated factor VIII level, factor V Leiden, PT 20210 A allele or heparin cofactor II deficiency was found in the present study. Homozygous MTHFR 677 CfwdarwT gene %mutation% was found in 7 patients (14%); one of them also had a plasminogen deficiency. No possible risk factor of venous thrombosis could be found in 24 patients (48%). In conclusion, malignancy and protein S deficiency were the most frequent acquired and congenital causes of venous thrombosis in the Chinese, respectively.

11/7/58  
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15379683 BIOSIS NO.: 200000097996  
%Resistance% to activated protein C and low levels of free protein S in Greek patients with inflammatory bowel disease  
AUTHOR: Koutroubakis I E (Reprint); Sfiridaki A; Mouzas I A; Maladaki A; Kapsoritakis A; Roussomoustakaki M; Kouroumalis E A; Manousos O N  
AUTHOR ADDRESS: Department of Gastroenterology, University Hospital Heraklion, 71110, Heraklion, Crete, Greece\*\*Greece  
JOURNAL: American Journal of Gastroenterology 95 (1): p190-194 Jan., 2000  
2000  
MEDIUM: print  
ISSN: 0002-9270  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: OBJECTIVE: Patients with inflammatory bowel disease (IBD) frequently suffer from thromboembolic events. A recently identified mechanism for thrombophilia, the poor anticoagulant response to activated protein C, has been suggested as one of the leading risk factors for thrombosis. The aim of this study was to evaluate the frequency of thrombophilic abnormalities, including activated protein C-

%%%resistance%%% (APCR), in Greek patients with ulcerative colitis (UC) and Crohn's disease (CD). METHODS: Forty-eight patients with UC, 36 with CD, and 61 matched healthy controls (HC) were studied. Cases with presence of lupus anticoagulant, use of anticoagulants or heparin, and pregnancy were excluded. Disease activity in CD was evaluated by use of the Crohns Disease Activity Index (CDAI) score and in UC by the Truelove-Witts grading system. Plasma levels of protein C, free protein S, %antithrombin% %III% (AT-III), activated protein C %resistance% (APCR), and fibrinogen were determined in IBD patients, as well as in HC. All the cases and controls with abnormal APCR were further studied by genetic testing for the factor V Leiden %mutation%. RESULTS: Mean fibrinogen levels in UC and CD patients were significantly elevated ( $p < 0.0001$ ), compared with HC. The mean values of free protein S, as well as mean APCR, were significantly lower in UC and CD patients than in the HC ( $p < 0.0001$ ). Seven (five UC and two CD) of 84 IBD patients (8.3%) and three of the HC (4.9%) had the factor V Leiden %mutation%. No significant difference was observed for the other thrombophilic parameters. Fibrinogen levels and profound free protein S deficiency were found related to disease activity. CONCLUSIONS: Thrombophilic defects are common in Greek patients with IBD and they could interfere either in the disease manifestation or in the thrombotic complications.

11/7/59

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15313902 BIOSIS NO.: 200000032215

The Factor V (Leiden) Test: Evaluation of an assay based on dilute Russell Viper Venom Time for the detection of the Factor V Leiden %mutation%

AUTHOR: Quehenberger Peter; Handler Sylvia; Mannhalter Christine; Kyrle Paul Alexander; Speiser Wolfgang (Reprint)

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JOURNAL: Thrombosis Research 96 (2): p125-133 Oct., 1999 1999

MEDIUM: print

ISSN: 0049-3848

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: In the present study a new clotting assay for the detection of an increased %resistance% of coagulation factor V against degradation by activated protein C (Factor V Leiden %mutation%, FVLM) was evaluated. The Factor V (Leiden) Test (Gradipore, North Ryde NSW, Australia) is based on the dilute Russell Viper Venom Time (DRVVT), which is prolonged when the plasma sample is preincubated with dilute whole Agkistrodon contortrix venom for activation of protein C (PC). In contrast to the DRVVT based global assay, Protein C Pathway Test (Gradipore, North Ryde NSW, Australia) this new assay is expected to be more specific for FVLM because of optimized amounts of the venom. The test result is expressed as the ratio between the DRVVT with and without addition of the venom. The following precision values were found: intraassay coefficient of variation (CV): 5.53% (n=20) in the normal range, 4.30% (n=20) in the pathological range; interassay CV: 6.90% (n=10) and 7.64% (n=10),

respectively. A normal range (5th to 95th percentile) of 2.12 to 3.08 was calculated from 50 healthy controls. A ratio below 2.12 was found in all samples from patients with FVLM (n=21), in 9 of 12 patients with PC, in 0 of 6 with protein S (PS), and in 0 of 4 with antithrombin (AT) deficiency. There was, however, a good discrimination between carriers of the FVLM (highest ratio 1.44) and patients deficient in PC (lowest ratio 1.59), in particular when samples were prediluted with factor V deficient plasma FVDP (1.16 vs. 1.96, respectively). Predilution of samples with FVDP caused a clear discrimination between controls and patients deficient in PC, PS, AT, and FVLM-positive individuals and also in patients on oral anticoagulant treatment. Our data show that the Factor V (Leiden) Test discriminates well between carriers of the FVLM and healthy controls or patients deficient in PC, PS, and AT. Individuals presenting values between the lower cutoff of controls and the range in which FVLM-positive individuals are found are highly suspicious for protein C deficiency.

11/7/60

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15310847 BIOSIS NO.: 200000029160

Thrombophilic factors and their relation to thromboembolic and other clinical manifestations in Behcet's disease

AUTHOR: Mader Reuven (Reprint); Ziv Michael; Adawi Muhammad; Mader Rivka; Lavi Idit

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JOURNAL: Journal of Rheumatology 26 (11): p2404-2408 Nov., 1999 1999

MEDIUM: print

ISSN: 0315-162X

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Objective. To evaluate the prevalence of thrombophilic factors known to induce intravascular clotting and to assess their relationship with thromboembolic complications and the other clinical manifestations in Behcet's disease (BD). Methods: Twenty-five patients with established BD were studied. Twenty patients with rheumatic conditions not known to be associated with venous or arterial thromboembolic phenomena served as controls. Eight of the patients with BD (32%) had either deep vein thrombosis (6 patients), arterial thromboembolic phenomena (2), or both (2). All participants were tested for IgG and IgM anticardiolipin antibody (aCL) levels, the presence of circulating lupus anticoagulant (LAC), protein C, protein S, and antithrombin activity, activated protein C resistance, and where appropriate factor V Leiden mutation. Results. Elevated levels of IgG aCL were detected in 10 (40%) patients with BD compared to one (5%) in the control group (p = 0.012). No significant differences were noted in the other variables studied between the 2 groups. No statistically significant correlation was found between any variable and the clinical manifestations. Conclusion. Patients with BD do not have decreased protein C, protein S, or antithrombin activity, activated protein C resistance, circulating LAC, or elevated levels of IgM aCL. A significant number of patients have elevated levels of IgG aCL but they

are not associated with venous or arterial thrombosis. No correlation was found between any variable and other clinical manifestations of the disease.

11/7/61

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15088932 BIOSIS NO.: 199900348592

Clinically symptomatic central venous catheter-related deep venous thrombosis in newborns

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JOURNAL: Acta Paediatrica 88 (6): p642-646 June, 1999 1999

MEDIUM: print

ISSN: 0803-5253

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The objective of this study was to evaluate the incidence of clinically symptomatic central venous catheter (CVC)-related deep venous thrombosis (DVT) in newborns and small infants and to try to identify clinical and genetic risk factors for catheter-related DVT among children with thrombotic complications. CVC was inserted in 44 consecutive infants (age range 0-90 d) during the period January 1990 to December 1995 in the neonatal intensive care unit (NICU) of Kuopio University Hospital in Kuopio. The symptoms of DVT were: syndrome of superior vena cava in 2, swelling at the CVC puncture site in 6 and repeated CVC obstructions in 2. The formation of DVT was verified by venography. Children with DVT (n = 10) had 26 (10-365, in total 623) catheter days compared with 9 d (1-155, in total 591) in patients without DVT (n = 26) (p < 0.005). The median (range) number of days from catheter insertion to diagnosis of DVT was 19 (7-210). CVC had to be removed from 11 (25%) children due to various complications. There was no DVT-related mortality. A positive family history with thromboembolic episodes at a young age was found in 3 of 10 families with a child suffering CVC-related DVT. The levels of coagulation inhibitors were evaluated at the age of 9-69 mo in all 10 (23%) children with CVC-related DVT. We detected no deficiencies in protein S, protein C or antithrombin. One child was heterozygous for the point mutation (R506Q) in the factor V gene known to cause activated protein C resistance (APCR). We conclude that newborns with CVC are at great risk of DVT and that the aetiology of DVT can rarely be identified via measurements of coagulation inhibitors.

11/7/62

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15056131 BIOSIS NO.: 199900315791

A possible role for activated protein C resistance in patients with first and second trimester pregnancy failure

AUTHOR: Tal Joseph (Reprint); Schliamser Liliana M; Leibovitz Zvi; Ohel Gonen; Attias Dina

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JOURNAL: Human Reproduction (Oxford) 14 (6): p1624-1627 June, 1999 1999  
MEDIUM: print  
ISSN: 0268-1161  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Thrombophilia was recently suggested as a possible factor in recurrent pregnancy losses. We studied prospectively 125 patients (mean age 31.4  $\pm$  5.6 years) with one or more first or second trimester pregnancy losses for the prevalence of activated protein C resistance (APCR). Proteins C and S antigens, antithrombin, antinuclear antibodies, anticardiolipin, and lupus anti-coagulant were also evaluated. Patients with uterine malformations, hormonal abnormalities, chromosomal translocations and infectious causes were excluded. A control group of 125 women with no past fetal loss were matched with the study group. Whenever the APC-sensitivity ratio (APC-SR) was  $\leq$  2.2, polymerase chain reaction for factor V mutation (Leiden) was performed. Heterozygosity for the mutation was found in 18 patients (14.4%) compared with seven heterozygous among 125 control group (5.6%;  $P < 0.05$ ). Acquired APCR (APC-SR 1.8 and Leiden negative) was revealed in seven patients (5.6%) in the study group and in three of the controls (2.4%; not significant). The rate of preclinical pregnancy losses (17/48) and second trimester miscarriages (10/48) in mutation carriers was significantly higher than in patients with no APCR (25/214) and (14/214) respectively ( $P < 0.001$  and  $P < 0.01$  respectively). Live birth rate was not different between the two groups. Occurrence of APCR with any kind of pregnancy loss calculated per patient, in our study group, was approx 1/7, 1/4 and 1/5 with one, two and three or more pregnancy losses respectively. These findings suggest that assessment of APCR should be considered in a more extended evaluation of such patients.

11/7/63

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14919054 BIOSIS NO.: 199900178714

Disorders in haemostatic parameters in pregnant women with factor V Leiden mutation and in her newborn

AUTHOR: Watala Cezary (Reprint); Golanski Jacek; Skrzypinska Danuta;  
Szaruga Barbara; Kowalska-Koprek Urszula; Pajszczyk-Kieszkiewicz Teresa;  
Bienkiewicz Andrzej; Chojnowski Krzysztof; Walus Mariusz; Pietrucha  
Tadeusz

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JOURNAL: Acta Haematologica Polonica 29 (4): p507-514 1998 1998  
MEDIUM: print  
ISSN: 0001-5814  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: Polish

ABSTRACT: Venous thrombosis with the event of pulmonary thromboembolism was recognised in a 32-yr old woman in the late III trimester (23. week) of her pregnancy. Based on the aPTT ratio in the activated-protein C resistance (APCR) test = 0.73), verified with polymerase chain reaction technique, the woman was diagnosed as a heterozygote for the factor V Leiden mutation. Using flow cytometry, we found significantly depressed platelet reactivity in the presence of agonists and activating factors, which may point to a considerable platelet consumption. Since diagnosed, the woman was subjected to a standard anticoagulant therapy, and no further signs of thromboembolism were revealed. The patient underwent an uncomplicated delivery by Caesarean section and there was no increased thrombotic activity during the first days of puerperium. The male newborn (heterozygote for Leiden mutation of factor V) had significantly reduced protein C and antithrombin activities (respectively 28% and 45%), whereas APCR ratio remained within a tolerance limit (RAccelerimat = 0.92). Also, prothrombin fragment 1 + 2 level (2.64 nM) was within a normal range for healthy newborns. His platelets were more reactive to activating agents compared to platelets of normal newborns, which are normally hyposensitive and hyporeactive in response to thrombin, thrombin receptor activating peptide and ADP. These platelets showed the characteristics intermediate between the cells originating from newborns and from adults.

11/7/64

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14898773 BIOSIS NO.: 199900158433

Laboratory evaluation of hypercoagulable states

AUTHOR: Van Cott Elizabeth M (Reprint); Laposata Michael

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JOURNAL: Hematology-Oncology Clinics of North America 12 (6): p1141-1166 Dec., 1998 1998

MEDIUM: print

ISSN: 0889-8588

DOCUMENT TYPE: Article; Literature Review

RECORD TYPE: Citation

LANGUAGE: English

11/7/65

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14817833 BIOSIS NO.: 199900077493

Primary thrombophilia in Mexico: A prospective study

AUTHOR: Ruiz-Arguelles Guillermo J (Reprint); Gonzalez-Estrada Sonai;

Garces-Eisele Javier; Ruiz-Arguelles Alejandro

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JOURNAL: American Journal of Hematology 60 (1): p1-5 Jan. 1, 1999 1999

MEDIUM: print

ISSN: 0361-8609

DOCUMENT TYPE: Article



RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: A group of 102 Mexican Mestizo patients with appropriate clinical features suggestive of primary thrombophilia was prospectively studied. Thirty-nine percent of them had activated protein C %%%resistance%%%, but only four patients displayed the factor V Leiden %%%mutation%%%. Five percent of the individuals were found to be protein C deficient, whereas 2% had protein S deficiency. No cases of abnormalities in %%%antithrombin%%%, plasminogen, tissue-type plasminogen activator or plasminogen activator inhibitor were found. The low prevalence of the activated protein C %%%resistance%%% genotype, probably stemming from the genetic admixture of the Mexican Mestizo group is noteworthy.

11/7/66  
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14801881 BIOSIS NO.: 199900061541  
Prevalence of the factor V Leiden %%%mutation%%% in children and neonates with thromboembolic disease  
AUTHOR: Hagstrom J Nathan (Reprint); Walter Johannes; Bluebond-Langner Rachel; Amatniek Joan C; Manno Catherine S; High Katherine A  
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JOURNAL: Journal of Pediatrics 133 (6): p777-781 Dec., 1998 1998  
MEDIUM: print  
ISSN: 0022-3476  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Objective: %%%Resistance%%% to activated protein C (APC) has been identified as a risk factor for thrombotic disease in adults. In over 90% of cases, the basis for the APC %%%resistance%%% is a %%%mutation%%% in the coagulation factor V gene (factor V Leiden) that renders the protein more resistant to inactivation by APC. We sought to determine the prevalence of the factor V Leiden (FVL) %%%mutation%%% in neonates and children who had experienced an arterial or venous thromboembolic event. Study design: We retrospectively analyzed the clinical records of 33 neonates and 52 children with thromboembolic disease. Screening for the FVL %%%mutation%%% was performed by DNA analysis, allowing for identification of patients as normal, heterozygous, or homozygous. Results: Of the 85 patients studied, 12 (14.1%) were heterozygous for FVL; none were homozygous. Of the 47 patients who had arterial central nervous system events, 8 (17%) were positive for the FVL %%%mutation%%%, including 6 of 22 (27%) neonates. Of those patients who had a venous thrombosis, 4 of 32 (12.5%) were FVL positive. None of the 85 patients had protein C deficiency, 3.5% had protein S deficiency, 1.2% had %%%antithrombin%%%, plasminogen, tissue-type plasminogen activator or plasminogen activator inhibitor deficiency, and 16.5% had anti-phospholipid antibodies. Conclusion: These data suggest that the FVL %%%mutation%%% plays a role in the development of arterial and venous thrombotic events in neonates and children.

11/7/67

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14712524 BIOSIS NO.: 199800506771

Prevalence of factor V Lieden (APCR) and other inherited thrombophilias in young patients with myocardial infarction and normal coronary arteries

AUTHOR: Dacosta A; Tardy-Poncet B; Isaaz K; Cerisier A; Mismetti P;

Simitsidis S; Reynaud J; Tardy B; Piot M; Decousus H; Guyotat D

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JOURNAL: Heart (London) 80 (4): p338-340 Oct., 1998 1998

MEDIUM: print

ISSN: 1355-6037

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Objective-To investigate the role of activated protein C  
%%resistance%% (APCR, factor V Leiden) in coronary artery thrombosis.  
Methods-The prevalence of APCR and of congenital deficiencies of  
%%antithrombin%% %%III%%, protein C, protein S, plasminogen and  
factor XII was investigated in adult patients under 45 years of age with  
acute myocardial infarction. The results were compared with those of a  
group of 53 age and sex matched control subjects. Results-Among 75  
patients under the age of 45 years who were admitted from November 1994  
to April 1996 for acute myocardial infarction, 22 (29.3%) had normal  
coronary arteriography (group I) and 53 (70.7%) had significant coronary  
artery disease (group II). Inherited thrombophilia was more often found  
in group I (4/22, 18.2%) than in group II (4/53, 7.5%) but the difference  
was not significant (F test:  $p = 0.22$ ). The prevalence of APCR was 9.1%  
(2/22) in group I, 3.8% (2/53) in group 2 ( $p = 0.57$ ), and 3.8% (2/53) in  
the normal control group ( $p = 0.57$ ). Conclusions-The prevalence of  
congenital thrombophilias, including APCR, does not seem to be increased  
in young patients with myocardial infarction and normal coronary  
angiograms, compared with young patients with coronary atherosclerosis  
and with normal control subjects. However, the statistical power of the  
study is too low to detect a significant difference and these results are  
published to allow a meta-analysis of this problem in the future.

11/7/68

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14593423 BIOSIS NO.: 199800387670

Cerebral venous sinus thrombosis in infancy and childhood: Role of genetic and acquired risk factors of thrombophilia

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JOURNAL: European Journal of Pediatrics 157 (7): p555-560 July, 1998 1998

MEDIUM: print

ISSN: 0340-6199

DOCUMENT TYPE: Article

RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: Over a 3 year period of R506Q mutation in the factor V (FV) FV:Q506 gene, FV, factor XII (FXII), prothrombin, protein C, protein S, antithrombin, heparin cofactor II, anticardiolipin antibodies and lipoprotein (a) (Lp(a)) were measured in 32 infants and children with sinus thrombosis. Heterozygous FV:Q506 (n = 5), homozygous FV:Q506 (n = 2), homozygous FXII deficiency (n = 1), protein C deficiency type I (n = 5), protein C deficiency type II (n = 1), antithrombin deficiency type I (n = 1) increased Lp (a) (n = 5), activated protein C-resistance without mutation in the FV gene (n = 2), and increased anticardiolipin IgG antibodies (n = 2) were diagnosed in the children investigated. In a further two patients we found combinations of increased Lp(a) with moderate hyperhomocystinaemia and heterozygous plasminogen deficiency with heterozygous FXII deficiency. In addition, increased anticardiolipin IgG antibodies were found in combination with heterozygous FV:Q506 (n = 1) and protein C type I deficiency (n = 2) respectively. Out of 32 patients with venous sinus thrombosis, 3 showed additional peripheral venous vascular occlusion. Contributing factors were present in 31 out of 32 patients investigated. Family members of 10 affected children had suffered from venous thrombo-embolism prior to the study. Conclusion: Our data suggest that additional contributing factors may promote manifestation of cerebral venous sinus thrombosis in infants and children with an inherited prothrombotic state. Further prospective studies are required to evaluate their potential role as "triggering" agents.

11/7/69

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14546166 BIOSIS NO.: 199800340413

Prevalence of prothrombin mutation in patients with venous thromboembolism

AUTHOR: Mayer B (Reprint); Koscielny J (Reprint); Baumann-Baretti B (Reprint); Stier C (Reprint); Kalus U (Reprint); Ziemer S; Kulozik A; Kieseewetter H (Reprint)

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JOURNAL: Annals of Hematology 76 (SUPPL. 1): pA72 1998 1998

MEDIUM: print

CONFERENCE/MEETING: 42nd Annual Meeting of the Gesellschaft fuer Thrombose- und Haemostaseforschung (Society for Thrombosis and Hemostasis Research) Frankfurt/Main, Germany February 25-28, 1998; 19980225

SPONSOR: Society for Thrombosis and Hemostasis Research

ISSN: 0939-5555

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LANGUAGE: English

11/7/70

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14546162 BIOSIS NO.: 199800340409

Activated protein C %%%resistance%%% in inflammatory bowel disease

AUTHOR: Altorjay I; Palatka K; Laszlo P; Boda Z; Udvardy M

AUTHOR ADDRESS: 2nd Dep. Med., Med. Univ. Sch., Debrecen, Hungary\*\*Hungary

JOURNAL: Annals of Hematology 76 (SUPPL. 1): pA71 1998 1998

MEDIUM: print

CONFERENCE/MEETING: 42nd Annual Meeting of the Gesellschaft fuer Thrombose- und Haemostaseforschung (Society for Thrombosis and Hemostasis Research) Frankfurt/Main, Germany February 25-28, 1998; 19980225

SPONSOR: Society for Thrombosis and Hemostasis Research

ISSN: 0939-5555

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LANGUAGE: English

11/7/71

DIALOG(R)File 5:Biosis Previews(R)

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14472774 BIOSIS NO.: 199800267021

A hypercoagulable state in activated protein C resistant patients with ischemic stroke

AUTHOR: De Lucia D (Reprint); D'Alessio D; Pezzella S; Maisto G; Di Mauro C ; Marotta R; Del Giudice V; Iacoviello L

AUTHOR ADDRESS: Inst. General Pathol. Oncol., Second Univ. Naples,

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JOURNAL: International Journal of Clinical and Laboratory Research 28 (1): p74-75 April, 1998 1998

MEDIUM: print

ISSN: 0940-5437

DOCUMENT TYPE: Letter

RECORD TYPE: Citation

LANGUAGE: English

11/7/72

DIALOG(R)File 5:Biosis Previews(R)

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14458942 BIOSIS NO.: 199800253189

Saphenous vein thrombophlebitis (SVT): A deceptively benign disease

AUTHOR: Hanson Judith N; Ascher Enrico (Reprint); Depippo Patrick; Lorensen Elke; Scheinman Marcel; Yorkovich William; Hingorani Anil

AUTHOR ADDRESS: Div. Vascular Surg., Maimonides Med. Center, 4802 Tenth Ave., Brooklyn, NY 11219, USA\*\*USA

JOURNAL: Journal of Vascular Surgery 27 (4): p677-680 April, 1998 1998

MEDIUM: print

ISSN: 0741-5214

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Purpose: The association between deep vein thrombosis (DVT) and the hypercoagulable state is a well-established entity. However, the association between saphenous vein thrombophlebitis and coagulation abnormalities has not been investigated. Although thrombosis of varicose

veins typically runs a benign course, phlebitis of the saphenous system may propagate to the deep system or saphenofemoral junction that requires more aggressive therapy. Given the potential similarity in clinical outcome between saphenous vein thrombophlebitis (SVT) and DVT, we have investigated the coagulation profile of patients presenting with isolated SVT. Methods: Seventeen consecutive patients who presented to our vascular laboratory with isolated SVT had a coagulation profile performed that included antithrombin (AT III), protein C (PC), protein S (PS) antigen and activity levels, activated protein C (APC) resistance, factor V DNA mutation, and coagulation factors II and X. All patients had duplex scans performed on both the superficial and deep venous systems. Patients with SVT only were treated with nonsteroidal antiinflammatory drugs (NSAIDs) and warm soaks as outpatients, whereas those patients found to have DVT or a clot at the saphenofemoral junction were fully anticoagulated with heparin and coumadin therapy. All 17 patients had at least one repeat coagulation profile performed up to 5 months after their SVT occurrence to ensure that the results of hypercoagulability were not transient. Results: Ten (59%) of the 17 patients with SVT had abnormal coagulation profiles on initial presentation. All 10 patients who were hypercoagulable had repeat tests and 6 (35%) remained abnormal. Four patients who had abnormal results converted to normal values. Seven patients with normal coagulation profiles on initial presentation had repeat tests and all remained normal. Conclusion: The incidence of the hypercoagulable state in patients with SVT is high. Thirty-five percent of patients with isolated SVT had consistently abnormal coagulation profiles. Patients with SVT may be prone to the development of DVT or saphenofemoral junction thrombophlebitis and should be closely followed after the initial diagnosis of hypercoagulability.

11/7/73

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14457310 BIOSIS NO.: 199800251557

Laboratory evaluation in venous thromboembolism

AUTHOR: Gaussem Pascale (Reprint); Siguret Virginie; Aiach Martine

AUTHOR ADDRESS: INSERM U. 428, Fac. Sci. Pharm. Biol., 4 Ave. de

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JOURNAL: Annales de Biologie Clinique 56 (1): p49-56 Jan.-Feb., 1998 1998

MEDIUM: print

ISSN: 0003-3898

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: French

ABSTRACT: Thromboembolic disease results from an hypercoagulable state and multifactorial causes may lead to hypercoagulability. Thrombogenic risk factors can be acquired and/or inherited. For each thrombophilic patient, the main clinical features retained are: the patient age, the familial history, the recurrence of thromboembolic events, an unusual site of thrombosis. Antiphospholipid antibodies, which are considered as acquired thrombogenic risk factors, can be detected with coagulation tests and/or Elisa methods. The association of antiphospholipid antibodies with thrombosis is defined as the antiphospholipid syndrome. Last decades, genetic risk factors were identified. First of all, antithrombin, protein

C and protein S deficiencies were described. These deficiencies are involved in about 10% of patients who develop thrombosis before the age of 50. In 1993, a new genetic risk factor was discovered: activated protein C %%%resistance%%% which is due to the Q506 %%%mutation%%% in factor V. This defect represents the most prevalent abnormality of inherited thrombophilia, affecting 20 to 40% of thrombophilic patients. Interestingly, hyperhomocysteinemia, known as potentially predisposing to arterial disease, was also recognized as a risk factor for venous occlusive disease. Several genes encoding homocysteine metabolism enzymes, such as cystathionine beta-synthase or methylenetetrahydrofolate reductase are concerned. Establishment of a causal association between the presence of a biological abnormality and the occurrence of thrombosis may lead to an adapted prophylaxis whatever the risk situation.

11/7/74

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14272721 BIOSIS NO.: 199800066968

Significance of thrombophilic disorders for "idiopathic" cerebral arterial infarction compared to venous thrombosis in children

AUTHOR: Becker S (Reprint); Heller C (Reprint); Lenz E; Gropp F; Kreuz W

AUTHOR ADDRESS: Centre Pediatr., Univ. Hosp., Frankfurt, Germany\*\*Germany

JOURNAL: Blood 90 (10 SUPPL. 1 PART 1): p150A Nov. 15, 1997 1997

MEDIUM: print

CONFERENCE/MEETING: 39th Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997; 19971205

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ISSN: 0006-4971

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LANGUAGE: English

11/7/75

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14266839 BIOSIS NO.: 199800061086

Primary thrombophilia in Mexican mestizos: A prospective study

AUTHOR: Ruiz-Arguelles G J (Reprint); Gonzalez-Estrada S; Garces-Eisele J; Ruiz-Arguelles A

AUTHOR ADDRESS: Centro Hematol. Med. Intern. Puebla, Lab. Clin. Puebla, Univ. Noreste at Tampico, Tampico, Mexico\*\*Mexico

JOURNAL: Blood 90 (10 SUPPL. 1 PART 2): p123B Nov. 15, 1997 1997

MEDIUM: print

CONFERENCE/MEETING: Thirty-ninth Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997; 19971205

SPONSOR: The American Society of Hematology

ISSN: 0006-4971

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RECORD TYPE: Citation

LANGUAGE: English

11/7/76

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14266832 BIOSIS NO.: 199800061079

The prevalence of hypercoagulable state among patients with chronic major vessel thromboembolic pulmonary hypertension

AUTHOR: Piovella F; Minzioni G; Emmi V; Serafini S; Barone M; Beltrametti C  
; Tosi P; D'Armini A; Barzaghi N; Siragusa S; Vigano M; Braschi A; Ascari  
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JOURNAL: Blood 90 (10 SUPPL. 1 PART 2): p121B Nov. 15, 1997 1997

MEDIUM: print

CONFERENCE/MEETING: Thirty-ninth Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997; 19971205

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LANGUAGE: English

11/7/77

DIALOG(R)File 5:Biosis Previews(R)  
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14266808 BIOSIS NO.: 199800061055

Budd Chiari syndrome and factor V Leiden mutation

AUTHOR: Hoffmann R (Reprint); Assy N; Baruch Y; Lanir N; Brenner B

AUTHOR ADDRESS: Dep. Hematol., Rambam Medical Cent., Haifa, Israel\*\*Israel

JOURNAL: Blood 90 (10 SUPPL. 1 PART 2): p116B Nov. 15, 1997 1997

MEDIUM: print

CONFERENCE/MEETING: Thirty-ninth Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997; 19971205

SPONSOR: The American Society of Hematology

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DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

11/7/78

DIALOG(R)File 5:Biosis Previews(R)  
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14245246 BIOSIS NO.: 199800039493

Hyperhomocysteinaemia and protein S deficiency in complicated pregnancies

AUTHOR: De Vries J I P (Reprint); Dekker G A; Huijgens P C; Jakobs C;

Blomberg B M E; Van Geijn H P

AUTHOR ADDRESS: Free Univ. Hosp., P.O. Box 7057, 1007 MB Amsterdam,  
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JOURNAL: British Journal of Obstetrics and Gynaecology 104 (11): p  
1248-1254 Nov., 1997 1997

MEDIUM: print

ISSN: 0306-5456

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

**ABSTRACT:** Objective. The aim of our study was to investigate whether women with placental abruption, intrauterine fetal death or small for gestational age infants have metabolic and/or haemostatic abnormalities which are known to be risk factors for intravascular thrombosis. Design. For two years blood tests were performed at > 10 weeks after delivery on all women without hypertensive disorders either before or during pregnancy, who had been consecutively admitted to our hospital with placental abruption, intrauterine fetal death and small for gestational age. Sample. A total of 62 women who had placental abruption (n = 31), intrauterine fetal death (n = 18) and a small for gestational age infant (n = 13). Setting. Obstetric outpatient clinic in a university hospital (Free University Hospital, Amsterdam). Methods. Presence of hyperhomocysteinaemia, various coagulation abnormalities and anticardiolipins was investigated. Results. Abnormalities were found in 20 women in the placental abruption group (20/31, 65%), in 10 women in the intrauterine fetal death group (10/18, 56%) and in 11 women in the small for gestational age group (11/13, 85%). Eight out of these 31 women had more than one abnormality. In the group of 62 women protein S deficiency was demonstrated in 26%, hyperhomocysteinaemia in 24%, Protein C deficiency in 6%, anticardiolipin IgG in 11%, anticardiolipin IgM in 5%, Lupus anticoagulant in 2%. An antithrombin III deficiency was not found. Thirty-three women were tested for activated protein C resistance (9% positive) and factor V Leiden mutation (6% positive). Hyperhomocysteinaemia was treated with a daily oral dose of 250 mg pyridoxine and 5 mg folic acid. After six weeks of vitamin supplementation homocysteine levels were tested again. At that time a mean reduction of fasting homocysteine value of 68% (95% CI 57-79) was found and of post-load value of 65% (95% CI 55-76). Conclusions. Based on the results of our study, it can be concluded that women whose pregnancies are complicated by either placental abruption, intrauterine fetal death or small for gestational age, even if there is no history of thrombo-embolic disorders or hypertension during pregnancy, should be advised to undergo an examination for metabolic and/or haemostatic abnormalities.

11/7/79

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14218405 BIOSIS NO.: 199800012652

Retinal arterial occlusion in a child with factor V Leiden and thermolabile methylene tetrahydrofolate reductase mutations

AUTHOR: Talmon T; Scharf J; Mayer E; Lanir N; Miller B; Brenner B (Reprint)

AUTHOR ADDRESS: Thrombosis and Hemostasis Unit, Dep. Hematol., Ramban Med. Center, Haifa 31096, Israel\*\*Israel

JOURNAL: American Journal of Ophthalmology 124 (5): p689-691 Nov., 1997

MEDIUM: print

ISSN: 0002-9394

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

**ABSTRACT: PURPOSE:** To analyze the potential cause of retinal arterial



occlusion in a 9-year-old child. METHODS: Case report. Antithrombin, protein C, free protein S, activated protein C resistance, and antiphospholipid antibodies in plasma were determined. Determination of factor V R506Q (Leiden mutation), thermolabile methylene tetrahydrofolate reductase by polymerase chain reaction, and restriction enzyme analysis were performed. RESULTS: The patient was found to be heterozygous for factor V R506Q (Leiden mutation) and homozygous for thermolabile methylene tetrahydrofolate reductase. CONCLUSION: Coexistence of two mild hereditary thrombophilic states may result in severe thrombotic manifestations in young people.

11/7/80

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14206297 BIOSIS NO.: 199800000544

Proposal for objective evaluation of the performance of various functional APC-resistance tests in genotyped patients

AUTHOR: Freyburger G (Reprint); Javorschi S; Labrousche S; Bernard P

AUTHOR ADDRESS: Lab. d'Hematol., Hopital Pellegrin, 33076 Bordeaux cedex, France\*\*France

JOURNAL: Thrombosis and Haemostasis 78 (5): p1360-1365 Nov., 1997 1997

MEDIUM: print

ISSN: 0340-6245

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The aim of the present study was to evaluate the relative performance of five screening methods for APC resistance caused by the factor V:Q506 mutation: the original method Coatest APC Resistance Chromogenix, a modified method using the same reagents but a predilution 1+4 of the plasma in a factor V deficient plasma from Stago (Stago deficient V) or from Chromogenix (V-DEF Plasma), the Coatest APC Resistance V (Chromogenix), and Accelerimat from bioMerieux. Normalization was done against a pool of normal plasmas for the methods from Chromogenix. The study included 350 subjects, 219 were genotyped (174 FV:R506R, 42 FV:Q506R, 3 FV:Q506Q) and most of them were assessed by more than one method. Uncertainty in predicting the FV genotype was evaluated by statistical analysis, which provided a way to quantitate the performance of the different diagnostic approaches. Performance of each test was evaluated by its sensitivity, specificity, R.O.C. curves, positive and negative likelihood ratios (LR), and the overall performance was determined by two parameters derived from the LR curves: the maximum LR value obtained at the crossover of the two curves, and the distance between the two curves for LR = 10. Coatest APC Resistance V and Accelerimat were proven to be the methods most able to discriminate for factor V:Q506, while normalization was not shown to improve the screening performance. The original method from Chromogenix was confirmed to undergo many influences (factor XII, PAI-1, thrombin-antithrombin complexes, antithrombin, protein C, hematocrit). Although a very good improvement was provided by the newest methods, they were shown to be influenced by protein S and/or factor V levels in the sample plasma.

11/7/81

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14200523 BIOSIS NO.: 199799834583

Budd-Chiari syndrome and factor V Leiden mutation

AUTHOR: Hoffman R (Reprint); Assy N; Brenner B; Enat R; Baruch Y

AUTHOR ADDRESS: Hematol. Unit, Rambam Med. Cent., Haifa, Israel\*\*Israel

JOURNAL: Hepatology 26 (4 PART 2): p205A 1997 1997

CONFERENCE/MEETING: 48th Annual Meeting of the American Association for the Study of Liver Diseases Chicago, Illinois, USA November 7-11, 1997;

19971107

ISSN: 0270-9139

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

11/7/82

DIALOG(R)File 5:Biosis Previews(R)

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14114064 BIOSIS NO.: 199799748124

Activated-protein-C resistance in cancer patients

AUTHOR: Green David (Reprint); Maliekel Kochurani; Sushko Elena; Akhtar

Rasheed; Soff Gerald A

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JOURNAL: Haemostasis 27 (3): p112-118 1997 1997

ISSN: 0301-0147

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Background: Resistance to activated protein C (aPC) is usually linked to factor V Leiden, but may occur in other disorders associated with hypercoagulability. In this study, we investigated the frequency of resistance to aPC in patients with advanced cancer and examined the relationship of aPC resistance to other markers of coagulation activation. Methods: Patients (n = 39) had an established diagnosis of advanced cancer, controls (n = 20) were healthy persons. aPC resistance was measured as the ratio of activated partial thromboplastin times with and without aPC (aPC-sensitivity ratio, aPC-SR). The factor V Leiden mutation was detected by a polymerase-chain-reaction based technique. Other assays were performed by standard laboratory methods. Data were analyzed using t tests and the Pearson correlation. Results: aPC-SR was below 2 SD for 5 of the cancer patients (13%), but none of the controls; only 1 of the 5 had the factor V Leiden mutation. aPC-SR was inversely correlated (p lt 0.01) with factor VIII and fibrinogen in patients and with prothrombin activation fragment 1.2 (F1.2) in controls. Patient factor VIII, von Willebrand factor, (vWF), fibrinogen, F1.2 and D dimer were all significantly increased (p lt 0.01); antithrombin, protein C and proteins were similar to controls. Factor VIII correlated with vWF (p lt 0.001) and F1.2 with d-dimer (p lt 0.001). Other associations (p lt 0.05) were observed between factor V and protein C, fibrinogen and protein C, factor V and antithrombin and protein C and antithrombin. Four cancer patients had a history of

thromboembolism; their aPC-SR was similar to that of patients without thrombosis. Of the several coagulation measures examined, only vWF was higher in the patients with thrombosis (p = 0.01). Interpretation: Cancer patients have evidence of intravascular coagulation and increases in procoagulants and may have aPC resistance. The aPC resistance is not due to factor V Leiden, but is rather associated with elevated levels of factor VIII and fibrinogen, and in itself does not predict thrombosis.

11/7/83

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14007525 BIOSIS NO.: 199799641585

Leiden factor V mutation in four patients with small bowel infarctions

AUTHOR: Heresbach Denis (Reprint); Pagenault Mael; Gueret Pierre; Crenn Pascal; Berre Nathalie Heresbach-Le; Malledant Yannick; Fauchet Renee; Horellou Marie-Helene; Silver Jack; Messing Bernard; Bretagne Jean-Francois

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JOURNAL: Gastroenterology 113 (1): p322-325 1997 1997

ISSN: 0016-5085

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The Leiden factor V mutation is observed in 20% of unexplained lower limb venous thromboses and involves substitution of the arginine residue at position 506 by glutamine (R506Q). It is known to decrease the anticoagulant activity of activated protein C. This case report describes 4 cases of small bowel infarction (SBI) associated with the presence of this mutation. Two cases of arterial and 2 cases of venous SBI were observed. Extensive assessment excluded the usual causes of SBI and plasma hypercoagulation syndrome (antithrombin deficiency, protein C, and protein S deficiency and myeloproliferative syndrome). An abnormal resistance to activated protein C was observed. Molecular analysis consisting of polymerase chain reaction amplification and digestion with MnlI showed that 2 patients were heterozygous and 2 were homozygous for the R506Q mutation. Despite familial history of thrombosis in only 1 patient, first- and second-degree relatives of 2 patients also had the presence of the mutation. Examination for the presence of abnormal resistance to activated protein C should be part of the etiological assessment of SBI. Its presence may warrant consideration of long-term anticoagulant therapy, especially for patients with shortened small bowel who are treated by home parenteral nutrition with deep venous access.

11/7/84

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13956397 BIOSIS NO.: 199799590457

Low prevalence of thrombophilic coagulation defects in patients with deep

vein thrombosis of the upper limbs  
AUTHOR: Ruggeri M; Castaman G; Tosetto A; Rodeghiero F (Reprint)  
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JOURNAL: Blood Coagulation and Fibrinolysis 8 (3): p191-194 1997 1997  
ISSN: 0957-5235  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: While many studies have demonstrated the pathogenetic role of inherited deficiency of natural clotting inhibitors in patients in the development of deep vein thrombosis of lower limbs, no data are available on the prevalence of these abnormalities in patients with upper vein thrombosis. In this study, antithrombin, protein C, protein S, plasminogen, resistance to activated protein C and factor V Leiden mutation were assayed in 27 consecutive patients with thrombosis of upper extremities. Only two patients (7.4%) showed a congenital defect (one patient with deficiency of protein C, confirmed by family study, and one patient with factor V Leiden mutation). Anticardiolipin antibodies were also measured and four patients (14.8%) had increased levels, confirmed on a subsequent occasion 3 months later. Eighteen out of 27 patients (67%) had a predisposing or triggering factor, thus emphasizing the role of physical stress in the development of upper vein thrombosis. At variance with what is observed in deep vein thrombosis of the lower limbs, inherited clotting abnormalities seem to be rarely responsible for upper vein thrombosis, whereas anticardiolipin antibodies and cancer are implicated in a significant proportion of cases.

11/7/85  
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13915008 BIOSIS NO.: 199799549068  
Activated protein C resistance (factor V Leiden) associated with thrombosis in pregnancy  
AUTHOR: Hallak Mordechai (Reprint); Senderowicz Judith; Cassel Aliza; Shapira Chen; Aghai Ester; Auslender Ron; Abramovici Haim  
AUTHOR ADDRESS: Dep. Obstet. Gynecol., Wayne State Univ./Grace Hospital, 6071 W. Outer Dr., Detroit, MI 48235, USA\*\*USA  
JOURNAL: American Journal of Obstetrics and Gynecology 176 (4): p889-893 1997 1997  
ISSN: 0002-9378  
DOCUMENT TYPE: Article  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: OBJECTIVE: Our purpose was to evaluate activated protein C resistance phenotype and genotype among patients with thrombosis during pregnancy and the puerperium. STUDY DESIGN: This observational study was conducted prospectively during a 2-year period (July 1993 to June 1995) in a preselected population. All patients admitted to our high-risk pregnancy unit with a diagnosis of deep vein thrombosis, pulmonary emboli, transient ischemic attack, and cerebrovascular accident during pregnancy and the puerperium were included. Prothrombin time,

partial thromboplastin time, fibrinogen levels, protein C, protein S, antithrombin, functional test for activated protein C resistance, and factor V Leiden mutation by polymerase chain reaction were performed on each patient. RESULTS: Fifteen patients were included. Seven (46.6%) patients were positive for activated protein C resistance (factor V Leiden). All other coagulation studies were negative for all patients. All patients with activated protein C resistance had a venous thrombotic event, deep vein thrombosis, or pulmonary emboli, and only one had a cerebrovascular accident on the basis of sagittal sinus thrombosis. Only two of the activated protein C resistance-negative patients had venous thrombosis (pulmonary emboli). The remaining six patients had transient ischemic attacks or cerebrovascular accidents. For the subgroup with venous thrombosis during pregnancy and the puerperium, the incidence of activated protein C resistance (factor V Leiden) was 78%. CONCLUSION: This study demonstrates the incidence of factor V Leiden in a selected population in whom thrombotic events developed during pregnancy and the puerperium. This small-scale study provides justification for a large cohort study that will identify women with factor V Leiden and determine their risk for thrombosis during pregnancy and the puerperium. We believe that factor V Leiden should be evaluated in conjunction with thrombotic events in the pregnant woman.

11/7/86

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13909677 BIOSIS NO.: 199799543737

Frequency of the factor V gene Leiden mutation in patients with thromboembolic disease: Analysis of 147 consecutive cases

AUTHOR: Lewandowski Krzysztof (Reprint); Turowiecka Zofia; Rozek Marek; Markiewicz Wojciech T; Zawilska Krystyna

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JOURNAL: Acta Haematologica Polonica 28 (1): p31-37 1997 1997

ISSN: 0001-5814

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: Polish

ABSTRACT: The frequency of the factor V gene Leiden mutation was evaluated in 147 consecutive patients with venous thromboembolic disease. In 28 patients (19%) the result of APC - resistance test was found to be abnormal. The presence of heterozygous form of mutation (G/A) was observed in 24 patients (16.3%). Additionally, in 4 cases (4%) protein C and in 4 other (4%) antithrombin deficiency was confirmed. Protein S deficiency was found in 13 patients (8.8%). The combined deficiencies of antithrombin and protein C and antithrombin and protein S were documented in two others patients. In one case the heterozygous form of the Leiden mutation was associated with protein S deficiency.

11/7/87

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13864927 BIOSIS NO.: 199799498987  
Natural anticoagulants and the liver  
AUTHOR: Castellino Daniel J; Salem Hatem H (Reprint)  
AUTHOR ADDRESS: Box Hill Hosp., Dep. Haematol. Oncol., Nelson Rd., Box  
Hill, VIC 3128, Australia\*\*Australia  
JOURNAL: Journal of Gastroenterology and Hepatology 12 (1): p77-83 1997  
1997  
ISSN: 0815-9319  
DOCUMENT TYPE: Article; Literature Review  
RECORD TYPE: Abstract  
LANGUAGE: English

ABSTRACT: The regulation of blood coagulation is dependent on a complex interplay between procoagulant, anticoagulant and fibrinolytic proteins. Most of these proteins are synthesized in the liver and their levels are altered in patients with liver disease. The liver also plays an important role in the regulation of haemostasis throughout the clearance of activated clotting factors. It is therefore not surprising that the critically balanced coagulation system is dysregulated in patients with liver disease. In moderate liver failure bleeding disorders predominate, whereas in more advanced liver disease intravascular coagulation is commonly observed and contributes to the overall dysregulation of blood coagulation. In some patients, liver disease can be primarily caused by an abnormality of the coagulation system. These patients usually have a hypercoagulable state caused by a deficiency of a component of the natural anticoagulant system. These include protein C, protein S and %antithrombin% %III%. More recently, activated protein C %resistance% caused by a point %mutation% in the Factor V gene has been identified as an important risk factor for thrombosis. In these patients the abnormal Factor V is resistant to cleavage by activated protein C resulting in ongoing uncontrolled procoagulant drive. Both hepatic and portal vein thrombosis have been reported in these patients. Appropriate management of these patients should include a thorough assessment of their natural anticoagulant proteins and exclusion of activated protein C %resistance% as the cause of their thrombotic disorder.

11/7/88  
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13845186 BIOSIS NO.: 199799479246  
APC-%resistance%, %antithrombin% %III%-deficiency and protein  
C- or S-deficiency  
AUTHOR: Winkler Ulrich H  
AUTHOR ADDRESS: Zentrum Frauenheilkunde, Univ. Essen, 45122 Essen, Germany  
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JOURNAL: Geburtshilfe und Frauenheilkunde 57 (1): p7-14 1997 1997  
ISSN: 0016-5751  
DOCUMENT TYPE: Article; Literature Review  
RECORD TYPE: Abstract  
LANGUAGE: German

ABSTRACT: Sensitivity, specificity and predictive values of potential screening tests for the prediction of thromboembolic complications in

pill users were calculated for the 6 million German pill users. In spite of high specificities, the predictive values of a positive family history, an **antithrombin** **III**-, protein C- or protein S-deficiency or **resistance** to activated protein C (APC) are low due to the very low absolute risk of thrombosis among pill users. More than half of the 840 yearly cases would pass the screening protocol undetected. A two-step screening protocol is suggested using the family history as selection criterium (reducing the need for laboratory screening by 85%) for laboratory investigation of APC sensitivity and **antithrombin** **III**-, protein C- and protein S-deficiency. Genotyping for factor V Leiden **mutation** is useful in cases with equivocal APC sensitivities or to confirm a homozygous genotype.

11/7/89

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13830129 BIOSIS NO.: 199799464189

Preeclampsia is associated with a reduced response to activated protein C

AUTHOR: Lindoff Claes (Reprint); Ingemarrson Ingemar; Martinsson Gunilla; Segelmark Marten; Thysell Hans; Astedt Birger

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JOURNAL: American Journal of Obstetrics and Gynecology 176 (2): p457-460 1997 1997

ISSN: 0002-9378

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: OBJECTIVE: **Resistance** to activated protein C is an inherited **mutation** of the coagulation factor V gene, a major factor predisposing to thromboembolic events. The purpose of this study was to investigate the occurrence of heterozygote and homozygote activated protein C **resistance** in women with preeclampsia. STUDY DESIGN: Activated protein C **resistance** and protein C and **antithrombin** **III** levels were determined in women (n = 50) with a history of preeclampsia and in controls (50 women with a previous normal pregnancy). The **mutation** of the factor V gene was analyzed. RESULTS: Activated protein C **resistance** was found in 22% of women with previous preeclampsia compared with 10% among controls. Two women in the previous preeclampsia group had a homozygote **mutation** of factor V; the others were heterozygous. There was a significant difference in the activated protein C ratio between women with previous preeclampsia and the control group, 2.6 +/- 0.4 versus 3.1 +/- 0.5 (p = 0.04). None of the women had protein C or **antithrombin** **III** deficiency. CONCLUSION: The results indicate that activated protein C **resistance** may be a contributory factor in the pathogenesis of preeclampsia.

11/7/90

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13400589 BIOSIS NO.: 199699034649

\*\*\*Resistance\*\*\* to activated protein C, the FV:Q-506 allele, and venous thrombosis

AUTHOR: Dahlback B (Reprint); Hillarp A; Rosen S; Zoller B

AUTHOR ADDRESS: Dep. Clin. Chem., Lund University, University Hosp.,  
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JOURNAL: Annals of Hematology 72 (4): p166-176 1996 1996

ISSN: 0939-5555

DOCUMENT TYPE: Article; Literature Review

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Vitamin K-dependent protein C is an important regulator of blood coagulation. After its activation on the endothelial cell surface by thrombin bound to thrombomodulin, it cleaves and inactivates procoagulant cofactors Va and VIIIa, protein S and intact factor V working as cofactors. Until recently, genetic defects of protein C or protein S were, together with \*\*\*antithrombin\*\*\* \*\*\*III\*\*\* deficiency, the established major causes of familial venous thromboembolism, but they were found in fewer than 5-10% of patients with thrombosis. In 1993, inherited \*\*\*resistance\*\*\* to activated protein C (APC) was described as a major risk factor for venous thrombosis. It is found in up to 60% of patients with venous thrombosis. In more than 90% of cases, the molecular background for the APC \*\*\*resistance\*\*\* is a single point \*\*\*mutation\*\*\* in the factor V gene, which predicts substitution of an arginine (R) at position 506 by a glutamine (Q). \*\*\*Mutated\*\*\* factor V (FV:Q-506) is activated by thrombin or factor Xa in normal way, but impaired inactivation of \*\*\*mutated\*\*\* factor Va by APC results in life-long hypercoagulability. The prevalence of the FV:Q-506 allele in the general population of Western countries varies between 2 and 15%, whereas it is not found in several other populations with different ethnic backgrounds. Owing to the high prevalence of FV:Q-506 in Western populations, it occasionally occurs in patients with deficiency of protein S, protein C, or \*\*\*antithrombin\*\*\* \*\*\*III\*\*\*. Individuals with combined defects suffer more severely from thrombosis, and often at a younger age, than those with single defects, suggesting severe thrombophilia to be a multigenetic disease.

11/7/91

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13103778 BIOSIS NO.: 199698571611

\*\*\*Resistance\*\*\* to activated protein C in healthy women taking oral contraceptives

AUTHOR: Olivieri Oliviero; Friso Simonetta; Manzato Franco; Guella Anna;  
Bernardi Francesco; Lunghi Barbara; Girelli Domenico; Azzini Margherita;  
Brocco Giorgio; Russo Carla; Corrocher Roberto (Reprint)

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JOURNAL: British Journal of Haematology 91 (2): p465-470 1995 1995

ISSN: 0007-1048

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: \*\*\*Resistance\*\*\* to activated protein C (APC) is at present



considered the most frequent laboratory abnormality in patients with deep-vein thrombosis. An increased risk for venous thrombosis is associated to the use of oral contraceptives (OC). We studied APC sensitivity in 50 healthy women taking OC and in 50 healthy controls, matched for age, smoking habit, educational and social levels, and the main biochemical routinary parameters. Subjects with a personal or familial history of thrombosis and also with chronic or acute diseases were excluded. Protein C, protein S, **antithrombin** **III** and lupus anticoagulant activity (LAC) were also evaluated. Increased fibrinogen and protein C levels, decreased protein S, and shortened PT and APTT were also observed in women taking OC. APC sensitivity ratio (APC-SR) was significantly lower in the OC group than in a control group ( $2.6 \pm 0.38$  v  $2.81 \pm 0.35$ ,  $P < 0.01$ ). Seven of eight women with APC ratio  $\leq 2$  (APC resistant) were OC users: the difference of prevalence was statistically significant (chi-squared test,  $P < 0.05$ ). Only two out of eight women were found heterozygous for the Leiden factor V **mutation**. Two APC-resistant women without the Leiden **mutation** subsequently discontinued OC and both then normalized their APC-SR. We conclude that acquired factors, i.e. oral contraceptives, may play an important role in determining plasma APC **resistance**.

11/7/92

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13074934 BIOSIS NO.: 199598542767

**Resistance** to activated protein C due to **mutated** factor V as a novel cause of inherited thrombophilia

AUTHOR: De Stefano Valerio (Reprint); Leone Giuseppe

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JOURNAL: Haematologica 80 (4): p344-356 1995 1995

ISSN: 0390-6078

DOCUMENT TYPE: Article; Literature Review

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Inherited **resistance** to activated protein C (APC) was recently recognized as a novel cause underlying venous thrombophilia. In most cases APC-**resistance** is due to a single point **mutation** in the factor V gene leading to a replacement of Arg506 with Gln (factor V Leiden). Amino acid substitution occurs at one of the APC cleavage sites of factor Va, rendering it resistant to APC inactivation. Plasma anticoagulant response to exogenous APC as a simple diagnostic assay of APC-**resistance** shows good sensitivity and specificity as compared to gene analysis, yet standardization of the results needs to be improved. The APC-**resistance** trait is present in 2%-6% of the general population and was found to be associated with venous thrombophilia in about 20% of patients with unexplained thrombosis. Clinical features are substantially similar to other congenital plasma abnormalities predisposing to thrombosis (**antithrombin** **III**, protein C, protein S deficiencies); yet the overall clinical penetrance of the defect seems lower, at least for the heterozygous condition. Preliminary data suggest a higher risk of thrombosis in APC-resistant homozygous individuals or in patients exhibiting APC-**resistance**

together with other thrombophilic genetic defects. To date, genetically determined APC-%%%resistance%%% does not seem to play a significant role in the development of arterial thrombotic disease.

11/7/93

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12778385 BIOSIS NO.: 199598246218

Factor V R5060 in patients with thrombophilia

AUTHOR: Radtke Klaus-P (Reprint); Greengard Judy S; Ehrenforth Silke (Reprint); Griffin John H; Zwinge Birga (Reprint); Lane David A; Scharrer Inge (Reprint)

AUTHOR ADDRESS: Univ. Clin. Frankfurt, Cent. Intern. Med., Frankfurt, Germany\*\*Germany

JOURNAL: Annals of Hematology 70 (SUPPL. 1): pA28 1995 1995

CONFERENCE/MEETING: 39th Annual Meeting of the Society for Thrombosis and Hemostasis Research Berlin, Germany February 15-18, 1995; 19950215

ISSN: 0939-5555

DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster

RECORD TYPE: Citation

LANGUAGE: English

11/7/94

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12752564 BIOSIS NO.: 199598220397

Factor V gene %%%mutation%%% causing inherited %%%resistance%%% to activated protein C as a basis for venous thromboembolism

AUTHOR: Dahlack B

AUTHOR ADDRESS: Dep. Clinical Chem., Univ. Lund, Malmo General Hosp., S-21401 Malmo, Sweden\*\*Sweden

JOURNAL: Journal of Internal Medicine 237 (3): p221-227 1995 1995

ISSN: 0954-6820

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Venous thromboembolism is often familial, suggesting that genetic risk factors are involved. Until recently, genetic defects known to predispose for thrombosis (deficiencies of %%%antithrombin%%% %%%III%%%, protein C, and protein S) had not been shown to account for more than 5-10% of the cases. Inherited %%%resistance%%% to the anticoagulant function of activated protein C (APC) in the last year has been identified as a major basis for familial thrombosis. Unlike other genetic risk factors for thrombosis, APC %%%resistance%%% is highly prevalent in the general population (2-5%). In more than 90% of cases, the APC-%%%resistance%%% phenotype is associated with a point %%%mutation%%% in the factor V gene, which predicts replacement of arginine at position 506 with a glutamine. As APC inhibits factor Va by cleavage at arginine 506. %%%mutated%%% factor V is resistant to APC. In its heterozygous state, the %%%mutation%%% is associated with a 5-10-fold increased risk of thrombosis. Homozygosity is associated with more severe APC %%%resistance%%%, and with a higher risk of thrombosis. Because of its

high prevalence in the population, individuals with deficiencies of other anticoagulant proteins occasionally carry the factor V gene %%%mutation%%%. People with such combinations of %%%mutations%%% have a higher risk of thrombosis than those with the single %%%mutations%%%. In conclusion, in the majority of familial thrombosis cases it is now possible to identify an underlying genetic risk factor. APC %%%resistance%%% caused by a single, factor V gene %%%mutation%%%, is the most frequent risk factor and it is at least ten times more common than any of the other genetic defects associated with thrombosis.

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            $246.10 107 Type(s) in Format  7
                $246.10 114 Types
$270.17 Estimated cost File5
    $2.40 TELNET
$272.57 Estimated cost this search
$272.57 Estimated total session cost   4.395 DialUnits
Logoff: level 05.20.01 D 11:29:24
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